P
Med
A

Biological
& Medical
Serials

ANNUAL REPORTS

OF THE

CHEMICAL LABORATORY

OF THE

AMERICAN MEDICAL ASSOCIATION

111

VOLUME 12. JAN.-DEC. 1919

LIBRARY
SEP 18 1945
UNIVERSITY OF TORONTO

Department
of
Pharmacology
University
Toronto

ANNUAL REPORTS

OF THE

CHEMICAL LABORATORY

OF THE

AMERICAN MEDICAL ASSOCIATION

VOLUME 12

JANUARY-DECEMBER, 1919

Department
of
Pharmacology
University
of
Toronto

LABORATORY STAFF
W. A. PUCKNER, PHAR. D., DIRECTOR
Secretary, Council on Pharmacy and Chemistry, A. M. A.
P. N. LEECH, PH. D.
A. H. CLARK, PH. G., B. S.
L. E. WARREN, PH. C., B. S.

PART I. . . . . REPRINT OF CONTRIBUTIONS
PART II. . . . REPORTS ABSTRACTED FROM THE JOURNAL
PART III. . . . . . REPORTS NOT PREVIOUSLY PUBLISHED

PRESS OF
AMERICAN MEDICAL ASSOCIATION
FIVE HUNDRED AND THIRTY-FIVE NORTH DEARBORN STREET
CHICAGO

PREFACE

The Chemical Laboratory of the American Medical Association was established in 1906 to assist the Association's Council on Pharmacy and Chemistry in the investigation of proprietary and unofficial nonproprietary medicinal preparations offered to the medical profession.

In accordance with the principles of its foundation, the Laboratory of the American Medical Association concerns itself primarily with the examination of those proprietary and unofficial medicinal preparations which the Council has under consideration. The Laboratory determines whether the claims made for the composition of these preparations are truthful, and establishes standards whereby the identity and purity of remedies admitted to the Council's publication "New and Nonofficial Remedies" may be determined.

In addition to the investigations made for the Council on Pharmacy and Chemistry, the activities of the Laboratory are directed in many other lines. It aids THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION in supplying the medical profession and the public with information about the character and composition of drugs. When requested, it reviews and verifies the chemical data contained in editorials and original contributions. It is often called on for information as to the character and composition of quack treatments and so-called "patent medicines." Through the columns of THE JOURNAL, and through direct correspondence, it responds to requests of physicians with information regarding the composition of medicines which they prescribe or in which they are interested. This volume contains accounts of those portions of the Laboratory's activities which are of interest to workers concerned with the examination and standardization of medicines. Special attention is called to the reports on the American-made synthetic drugs: barbital and barbital sodium, veronal and veronal sodium, luminal and luminal sodium, and phenetidyl-acetphenetidin hydrochlorid, also to the examination of acriflavine and proflavine which received considerable attention during the war in the treatment of wounds. It is hoped that these studies may be an incentive to manufacturers toward the elaboration of definite standards for the drugs which they manufacture.

Department
of
Pharmacology
University
of
Toronto

CONTENTS

PAGE
Preface 3
Examination of Procain, Barbital, Phenetidyl-Acetphenetidin, Cinchophen or Phenylcinchoninic Acid, Manufactured under Federal Trade Commission Licenses by Paul Nicholas Leech, Ph.D., William Rabak, Ph.G., Sc.B., and A. H. Clark, Ph.G., Sc.B......... 7
Iodin in Liquid Petrolatum by A. H. Clark, Ph.G., Sc.B. 21
A Note on a Very Old Specimen of Pepsin by L. E. Warren, Ph.C., B.S............................. 23
Nature's Remedy Tablets by A. H. Clark, Ph.G., B.S... 25
Cerelene 30
Depilagiene 31
Cuprase 32
Collosol Cocaine 33
Lane's Asthma Cure.. 35
The Dr. D. A. Williams Rheumatic Treatment......... 37
Collosols 42
Dr. De Sanctis' Rheumatic and Gout Pills............. 46
Dr. Miles' Heart Treatment........................... 49
Lavoris 53
Mocajah's Wafers and Micajah's Suppositories......... 55
Chloron, Chlorax and Number "3"...................... 57
Note on Melting Point of Acetylsalicylic Acid by Paul Nicholas Leech, Ph.D........................... 62
The Examination of Acriflavine and Proflavine by L. E. Warren, Ph.C., B.S............................ 64
The Examination of Commercial Barbital-Sodium by L. E. Warren, Ph.C., B.S............................ 70
The Examination of Luminal and Luminal-Sodium by L. E. Warren, Ph.C., B.S............................ 77
Barium Sulphate for Roentgen-Ray Work by A. H. Clark, Ph.G., Sc.B............................ 81
Benzyl Benzoate 84
The Examination of American-Made Chinosol.......... 87
The Examination of Apothesine......................... 88

Acidol and Acidol-Pepsin 91
Sodium Di-Oxide, Dental 93
Restoria 95
The Relative Permanency in Moist Air of Pilocarpin Hydrochlorid and Pilocarpin Nitrate 96
Sajodin 97
Curtis' Sacred Bark Root and Herb Compound 102
Gueth's Cancer Cure 103
Iodex and Liquid Iodex 104
I. G. O. 106

Department
of
Pharmacology
University
of
Toronto

PART I

REPRINTS OF CONTRIBUTIONS FROM THE CHEMICAL LABORATORY OF THE AMERICAN MEDICAL ASSOCIATION

AMERICAN-MADE SYNTHETIC DRUGS—II

Examination of Procain (Novocain), Barbital (Veronal), Phenetidyl-Acetphenetidin (Holocain), Cinchophen or Phenylcinchoninic Acid (Atophan), Manufactured under Federal Trade Commission Licenses *

Paul Nicholas Leech, Ph.D., William Rabak, Ph.G., Sc.B. and A. H. Clark, Ph.G., Sc.B., Chicago

(*Reprinted from The Journal A. M. A., Sept. 6, 1919, p. 754*)

Before European hostilities, the United States was so dependent on Germany for synthetic drugs that the dependence was considered a necessity; this was strikingly manifested by the precipitous rise in prices immediately after the embargo was declared against Germany. Since then the shortage of German-made synthetics has caused two important results: 1. The physician can do without most of the German drugs, because the pre-war demand had been stimulated artificially. 2. Those few synthetics which were in great need are being rapidly replaced by the American-made drugs.[1] In connection with the second result, the Chemical Laboratory of the American Medical Association has endeavored to contribute its services.

In September, 1917, it was announced[2] that the A. M. A. Chemical Laboratory would make studies of American-made synthetics. Just prior to this announcement, the National

---

* The first article of this series dealt with the purity of acetylsalicylic acid. Leech, P. N.: Examination of American-Made Acetylsalicylic Acid, J. Indust. & Engin. Chem., April, 1918, p. 288. "What's in a Name?" ibid., p. 255. Acetylsalicylic Acid, or "What's in a Name?" Editorial. J. A. M. A. **70**: 1097 (April 13) 1918. Annual Reports of the Chemical Laboratory of the American Medical Association, Vol. 11, 1918, p. 7.

1. Stieglitz, Julius: Synthetic Drugs, II, J. A. M. A. **70**: 688 (March 9) 1918. Leech, P. N.: The Vindication of the American Chemist; Synthetic Drugs, Chicago Chem. Bull., January, 1918, p. 230.

2. The Quality of American-Made Synthetics, J. A. M. A. **69**: 1018 (Sept. 22) 1917.

Research Council established a committee on synthetic drugs[3] "to facilitate the manufacture of synthetic drugs in this country and thus to relieve shortage and reduce the exorbitant prices which have resulted from the war."[4] Also during this time Congress was considering the "trading with enemy" act, first known as the Adamson bill—the purpose of which was to confer authority on the President to license American firms to use U. S. patents owned by German subjects. The act became law, September 28; the Federal Trade Commission was designated by the President to carry out the provisions of the law as it referred to enemy-owned patents. As a result of a conference, Oct. 30, 1917,[5] with various agencies, the Federal Trade Commission decided to consider licenses for manufacturers of synthetic drugs, *after* recommendations had been made by the Committee on Synthetic Drugs of the National Research Council; this committee in turn invoked the aid of the A. M. A. Chemical Laboratory in testing the manufacturer's products. The essence of the laboratory's work up to July 1, 1919, is reported in this paper.

THE NAMING OF LICENSED DRUGS

"Partly in order to help insure to licensees a market for their products after the war, in larger part inspired by the idea of encouraging the establishment of a permanent American industry in these important articles, the [Federal Trade] Commission wisely decided that American houses should be put on the same footing as competing foreign houses for after-the-war competition, by imposing on all licensees the obligation to use *new official names* for the articles, names which after the war will be open to all competitors, domestic and foreign."[6]

The new American names are:

Arsphenamin[7] (contracted from the scientific name arsenphenolamin) for salvarsan, arsenobenzol, diarsenol, arsaminol.

---

[3] This committee is composed of Julius Stieglitz, chairman, professor of chemistry, University of Chicago; W. A. Puckner, secretary of the Council on Pharmacy and Chemistry, American Medical Association, and Moses Gomberg, professor of chemistry, University of Michigan.

[4] Stieglitz, Julius: Shortage of Synthetic Remedies, J. A. M. A. **69**: 400 (Aug. 4) 1917.

[5] Foreign Patents to Be Open to American Manufacturers, J. A. M. A. **69**: 1550 (Nov. 3) 1917.

[6] For an interesting discussion, see Stieglitz, Julius: Synthetic Drugs, J. A. M. A. **70**: 536 (Feb. 23); 688 (March 9); 923 (March 30) 1918. Bracken, L. L.: Federal Trade Commission Requests Use of Official Names, ibid. **70**: 558 (Feb. 23) 1918.

Barbital (contracted from the scientific name diethyl-barbituric acid) for veronal.

Barbital-sodium (the sodium salt of barbital) for "veronal-sodium" and "medinal."

Cinchophen for atophan or phenylcinchoninic acid (the U. S. P. IX name).

Procain for novocain hydrochlorid (from "pro" and "(co)caine").

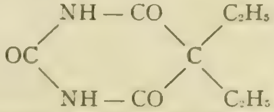
Procain nitrate for novocain nitrate.

EXAMINATION OF SYNTHETIC DRUGS

In testing chemically the products which had been submitted to the Federal Trade Commission, the aims were that the product should conform to a high degree of purity; at the same time the candidate for license should not be inflicted with undue hardships in making the product, such as an unnecessarily high degree of purity. It was insisted that the purity of the drugs should be equal to, if not greater than, that of the respective former German-made products, in order to uphold the name and reputation of the American manufacturers in the after-the-war competition. Consequently, in the chemical work the American product was always examined parallel with the German-made product, authentic samples of which latter the laboratory had in its possession. Whenever possible, the tests described in books of standards were carried out.

BARBITAL (VERONAL)

Barbital was introduced into medicine under the proprietary name "veronal," and was manufactured in Germany by Friedr. Bayer & Co., Leverkusen, and E. Merck & Co., Darmstadt, Germany. Barbital is descibed in New and Nonofficial Remedies 1919[8] as diethylbarbituric acid (diethylmalonyl urea) having the formula:



---

[7] The testing and standardizing of arsphenamin is being done by the Hygienic Laboratory, U. S. Public Health Service. For chemical tests see reprint 472, Public Health Reports. For a review of the patent literature see article by H. F. Lewis, J. Indst. Engin. Chem., Feb. 1, 1919, p. 141.

[8] New and Nonofficial Remedies. 1919, published by The Council on Pharmacy and Chemistry of the American Medical Association, p. 82.

It is official in the British Pharmacopeia under the name "barbitone," and in the German Pharmacopeia as "acidum diethylbarbituricum." Barbital "may be prepared by the interaction of esters of diethylmalonic acid with urea in the presence of metallic alcoholates. . . . It is also obtained by condensation of diethylcyanacetic ester with urea by means of sodium alcoholate." Barbital is used in medicine chiefly as a hypnotic.

The different brands of barbital which were submitted to the laboratory were subjected to the tests given in the books referred to above.[9] The products were:

1. Barbital (Abbott) Sample A, to Federal Trade Commission.

TABLE 1.—MELTING POINT

		Ash			Ash
1	188.5-189.0	0.01	5	188.0-188.5	0.01
2	188.5-189.0	0.01	6	188.0-188.5	0.01
3	188.0-188.5	0.01	7	188.0-188.5	0.01
4	188.0-188.5	0.04	8	188.0-188.5	0.02

2. Barbital (Abbott) Sample B, to Federal Trade Commission.

3. Barbital (Abbott) Sample C, to Red Cross.

4. Barbital (Antoine Chiris), to Federal Trade Commission.

5. Barbital (V. Halter), to Federal Trade Commission.

6. Barbital (Rector Chemical Company), to Federal Trade Commission.

7. Diethylbarbituric acid (Merck), to Council.

8. "Veronal," manufactured by Farb. vorm. Fried. Bayer & Co., Germany.

All responded satisfactorily to the tests. In Table 1 are given the respective melting points and percentages of ash found. (The melting point of a mixture of the sample with the original "veronal" was always taken.)

Barbital does not seem to form an insoluble salt with chlorplatinic acid; nor an ether-insoluble hydrochlorid or oxalate; nor an insoluble barium salt. It does not respond to many urea tests, and is not affected by urease as would be expected in light of the extensive investigations made on this enzyme by Van Slyke and Cullen.

As barbital is also sold in the form of tablets or mixtures, a reliable method for its quantitative determination in the presence of other substances is needed. Some experiments in this direction were made, but the press of other work did not permit their continuation. When time permits this work will be resumed.

---

[9] The pharmaceutic monograph on barbital has been omitted. It was published in the 1918 edition of the Annual Reports of the Chemical Laboratory of the American Medical Association.

At the time of writing this article, licenses for manufacture had been granted by the Federal Trade Commission to the Abbott Laboratories, to Antoine Chiris Company, and to the Rector Chemical Company.

BARBITAL SODIUM (MEDINAL OR VERONAL-SODIUM)

Barbital sodium, formerly sold under the proprietary names "veronal-sodium" and "medinal," is, as the former name suggests, the sodium salt of diethylbarbituric acid. Its therapeutic advantages are stated to be that more rapid results are obtained because of its increased solubility over barbital alone.[10] Barbital sodium should yield, according to theory, 11.19 per cent. of sodium and 89.31 per cent. of diethylbarbituric acid. A number of years ago, when "veronal-sodium" and "medinal" were being introduced, Puckner and Hilpert[11] found that these products yielded results corresponding closely to the theoretical amounts of sodium and diethylbarbituric acid. A recent examination of veronal-sodium, Merck, made for the Council on Pharmacy and Chemistry, showed it to be of the same composition as that previously reported.

Only one firm's product has been submitted to the laboratory through the Committee on Synthetic Drugs, but because of the unsatisfactory results, it was not recommended for license, nor, as far as we are aware, has the firm investigated its anomalies.[12] The amount of moisture in this specimen was 0.04 per cent. It yielded 10.94 and 10.97 per cent. of sodium. Puckner and Hilpert found 11.02 per cent. of sodium in "medinal," and 11.01 per cent. of sodium in "veronal-sodium." The theoretical amount, according to the formula given for medinal by the proprietors $(C_2H_5)_2CCONNaCONHCO$ is 11.19 per cent. When an aqueous solution of barbital sodium was acidified, and the diethylbarbituric acid extracted with ether, it was found that the amount of freed acid extracted varied directly with the length of time after acidification.

---

[10] New and Nonofficial Remedies, 1918, p. 96.

[11] Puckner, W. A., and Hilpert, W. S.: Veronal-Sodium and Medinal, J. A. M. A. **52**: 311 (Jan. 23) 1909; Rep. A. M. A. Chemical Lab., **2**: 13.

[12] Since this was written, the Council on Pharmacy and Chemistry has also accepted "Barbital-Sodium Abbott."

It is possible that in preparing the sodium salt of diethylbarbituric acid, the ring opens up, forming a compound not so easily affected by dilute mineral acids.

TABLE 2.—EXTRACTION OF A SAMPLE OF BARBITAL SODIUM

	Length of Time	Diethylbarbituric Acid per Cent.
a.	Immediately	75.5
a¹.	¾ hour	82.0
b.	Immediately	82.0
c.	1½ hours	80.5
d.	4 hours	82.82
e.	4 hours	83.56
f.	4 hours	83.41
g	45½ hours	84.89
h.	45½ hours	84.73
Theory	....	89.31
Veronal-Sodium	(Puckner and Hilpert)	89.01 (average)
Medinal	(Puckner and Hilpert)	88.95 (average)

PHENETIDYL-ACETPHENETIDIN HYDROCHLORID[13]
(HOLOCAIN HYDROCHLORID)

Phenetidyl-acetphenetidin hydrochlorid was introduced in the United States under the name "holocain hydrochloride" by Farbwerke, vorm. Meister Lucieus and Bruening, Hoechst-am-Main, Germany; the product apparently had not been patented in this country, although it was protected in Germany under patents No. 78,868 and 80,568. New and Nonofficial Remedies, 1918, describes "holocain hydrochlorid" as ethenyl - paradiethoxy - diphenyl - amidin hydrochlorid $CH_3 : (NC_6H_4OC_2H_5)\ (NHC_6H_4OC_2H_5)HCl$. It is used as a local anesthetic for the eye.

The standards, such as had been described, were meager and unsatisfactory. Hence when the first specimen of American-made phenetidyl-acetphenetidin was sent to the A. M. A. Chemical Laboratory through the agency of the Federal Trade Commission and the Committee on Synthetic Drugs, it was necessary for the laboratory to work out adequate standards.[14] As a result of the chemical work, a rather comprehensive monograph was drawn up, which was published in the 1918 Laboratory Reports. A summary of the products examined, with some of the chemical data, is given in Table 3. It will be seen that one specimen had a deficiency of about 2 per cent. of free base.

---

[13] No short, scientific name has been given for this substance although several are under consideration.

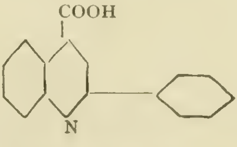
[14] Certain chemical tests are described by E. H. Rankin, Indian J. M. Res. **4**: 237, 1916; also Chem. Abst. **10**: 524. Other references are Schmidt: Pharmateutische Chemie **2**: 990. Beilstein II, (403). Arends, G.: Neue Arzneimittel und pharmazeutische Spezialitäten, Ed. 4, 1913, p. 271.

The melting point of the free base is given by a number of writers at 121 C. Although Kennert [15] stated it to be 117 C. and not 121 C., his findings seemingly went unheeded. It will be noted that our work shows the melting point to be in accord with that announced by Kennert.

The Federal Trade Commission has not issued any licenses for the manufacture of "holocain hydrochlorid." The John T. Milliken Company has withdrawn its application. The H. A. Metz Laboratories (Successor to Farbwerke Hoechst Company, New York) are making the product in this country.

CINCHOPHEN (PNENYLCINCHONINIC ACID, U. S. P.; ATOPHAN)

Cinchophen (phenlycinchoninic acid) was introduced in the United States as a medicine under the proprietary name "atophan," by Shering and Glatz, New York City, who before the war were the American agents for the German maufacturers "Chemische Fabric auf Actien von E. Schering, Berlin." Phenyl-cinchoninic acid (2 phenyl-quinolin-4 carboxylic acid) was first described by Doebner and Gieseke [16] in 1887, who prepared it by warming together pyro-racemic acid, benzaldehyd and anilin in alcoholic solution; it has the structural formula:



The chief use of phenylcinchoninic acid is as an antiuric acid agent, especially indicated in gout.

In 1913, the German house of Schering was made the assignee of patent 1,045,759 granted by the United States government [17] for the manufacture of phenylcinchoninic acid; at about the same time the product was admitted to the U. S. Pharmacopeia IX, under very loosely constructed standards.

---

[15] Kennert: Chem. Zentralbl. **2**: 556, 1897.
[16] Doebner and Gieseke: Ann. d. Chem. (Liebigs) **240**: 291, 1887.
[17] The validity of this patent is to be doubted.

TABLE 3.—DATA ON PHENETIDYL-ACETPHENETIDIN HYDROCHLORID

Manufacturer	Appearance	Moisture	Melting Point	Phosphorus Compounds	Phenetidin[*]	Indol Reaction	Ash	Per Cent. Base by Weight	Per Cent. Base by Titration	Melting Point of Base	Per Cent. Platinum in Platinum Salt[†]
John T. Milliken Co.	White crystalline powder	5.13	191.5 to 192	Absent	Negative	Positive	0.00	89.16	89.16	116 to 117	19.02
Synthetic Products Co.	White crystalline powder	2.90	192 to 192.5	Absent	Negative	Positive	0.13	87.49	87.26	116 to 117	19.3
H. A. Metz Laboratories, Inc.	White crystalline powder	4.99	192 to 192.5	Absent	Negative	Positive	0.00	89.14	88.55	117	19.34
Farbwerke-Hoechst Co. .... (German specimen)	Slightly pink crystal	5.09	190 to 191	Absent	Negative	Positive	0.16	89.65	89.64	116 to 117	19.00

---

[*] The phenetidin test is not very sensitive.

Some time after the beginning of the European war the proprietary "atophan" became scarce in America. In 1917, however, Schering and Glatz, New York, placed American-made atophan on the market and submitted it to the Council on Pharmacy and Chemistry. Later, other firms began to manufacture the product and also submitted specimens.

TABLE 4.—MELTING POINTS AND ASH

Product No.	Manufacturer	Melting Point, C.	Ash, %
1	Abbott Laboratories, Chicago	208.5–210.5	0.05
2	Abbott Laboratories, Chicago	212 –213	0.05
1	Calco Chem. Co., Bound Brook	209 –210.5	0.07
1	Morgenstern, New York	204.5–207.5	2.8
2	Morgenstern, New York	209.5–211.5	None
1	Schering and Glatz, New York	206 –208	None
2	Schering and Glatz, New York	209 –211	None
3	Schering and Glatz, New York	208.5–210	0.17
4a	Schering and Glatz, New York (1)	208.5–210	0.2
4b	Schering and Glatz, New York (2)	208.5–209.5	0.3
4c	Schering and Glatz, New York (3)	208.5–210	0.025
1	Wm. H. Sweet and Co., Columbus	204 –208	None
2	Wm. H. Sweet and Co., Columbus	209.5–211.5	0.04
1	German specimen from Schering and Glatz	210 –212	None

During the time it was investigating these products, the Federal Trade Commission decided that a license was needed to manufacture phenylcinchoninic acid under the patent just referred to, so that altogether the laboratory had a number of specimens to examine.

In making the examinations for the Council, the laboratory was practically confined, by virtue of the Food and Drugs Law, to limit its requirements of purity to those of the Pharmacopeia. Practically, the only tests were melting point, ash and solubility. According to the U. S. Pharmacopeia the melting point is "about 210." In New and Nonofficial Remedies, 1918, it was explained that atophan "complies with the standards for phenylcinchoninic acid, U. S. P., but melts between 208 and 212 C." The U. S. Pharmacopeia requires that no weighable ash remains on incinerating about 0.5 gm. of phenylcinchoninic acid. Considerable variations, especially in melting points, were found, as can be seen from Table 4.

By referring to this table on melting points and ash content it will be noted that the production of a better grade of products resulted after the respective firms had submitted samples to the A. M. A. Chemical Laboratory for criticism, and from a chemical standpoint, the last products examined were found to be as satisfactory as the German-made "atophan."

Solubility of Cinchophen (Phenylcinchoninic Acid). — As methods of determining impurities, or estimating the degree of purity of phenylcinchoninic acid were not described in the U. S. Pharmacopeia, it was decided to try extraction methods.[18] This in turn led to the question of solubilities. The U. S. Pharmacopeia gives the solubility of phenylcinchoninic acid only in general terms; hence it was deemed advisable to determine its solubilities and describe them in more definite terms. The sample of phenylcinchoninic acid employed to determine the solubility was obtained by repeated recrystallization from alcohol of a commercial specimen. Solubilities were determined in water; 95.0 per cent. alcohol; 48.5 per cent. alcohol;[19] chloroform and ethyl acetate.[20] Complete saturation of the solvent was attained according to the U. S. P. IX method (p. 599). The bath was maintained at a temperature of 25 C., with a range of ± 0.2 degrees. The solution was analyzed by the method of Seidell.[21] The data obtained for the solubility of phenylcinchoninic acid are given in Table 5.

TABLE 5.—SOLUBILITY OF CINCHOPHEN

Solvent	Gm. per Hundred Gm. of Sat. Solution	Solubility, Parts by Weight
Distilled water	0.0160	1 in 6,216.0
95 per cent. ethyl alcohol	0.8343	1 in 119.0
Dilute ethyl alcohol	0.0875	1 in 1,142.6
Chloroform	0.1075	1 in 929.7
Ethyl acetate	1.4151	1 in 70.6

The Abbott Laboratories, Chicago, have been licensed by the Federal Trade Commission to manufacture cinchophen. Other firms, however, have decided to manufacture it without the formality of obtaining a license, evidently considering the German-obtained patent not to be valid.[22]

---

18. Attempts were made to make salts of phenylcinchoninic acid with metals such as copper, mercury, barium and calcium, and also the chloroplatinic acid or periodid addition products. Reliable quantitative results could not be obtained.

19. This corresponds to "diluted alcohol, U. S. P."

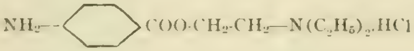
20. The ethyl acetate was Merck's product (redistilled), stated to contain 81.6 per cent. of ethyl acetate, 10 per cent. alcohol and alcohol derivatives.

21. Seidell, A.: Bull. 67, Hyg. Lab., U. S. P. H. S., p. 11.

22. Very recently the Chemical Foundation, Inc., has undertaken to grant licenses for cinchophen. The Calco Chemical Company has obtained one.

PROCAIN (NOVOCAIN)

Procain was introduced in medicine under the proprietary name "novocain," and before the war was obtainable in this country only through the Farbwerke Hoechst Company, the American representative of the German establishment, Farbwerke vorm. Meister Lucius Bruening, Hoechst a. M. Chemically it is the mono-hydrochlorid of para-amino-benzoyl-diethyl-amino-ethanol, having the structural formula:



It is prepared, according to U. S. patent No. 812,554 (issued to Alfred Einhorn, Munich, Germany) by treating para-nitro-benzoylchlorid with ethylene chlorhydrin and diethylamin with subsequent reduction of the nitro groups, the resulting product being purified by recrystallization.

Procain is employed largely in infiltration anesthesia. It is less toxic than cocain but its anesthetic action is not sustained. This drawback is overcome by the simultaneous injection of epinephrin and for this reason procain is often compounded with epinephrin in tablets, thus obviating the necessity of separate solutions.

When the first specimens of the American-made product were submitted through the channels of the Federal Trade Commission, it was necessary to compile a monograph.[23] This was prepared from descriptions in the available literature, mostly from tests described in New and Nonofficial Remedies, 1918, and the German Pharmacopeia V.

The submitted products were found satisfactory chemically. The toxicity determinations made by Dr. R. A. Hatcher, with the assistance of Dr. Carey Eggleston[24] indicated that none of the specimens are to be considered dangerous when used in ordinary dosage for normal individuals. Therefore the Federal Trade Commission, on recommendation of the Committee on Synthetic Drugs of the National Research Council (aided by the A. M. A. Chemical Laboratory), issued licenses for the manufacture of procain to the Farbwerke-Hoechst Company (which license was later transferred to the H. A. Metz Laboratories), to the Abbott Laboratories, to the Calco Chemical Company and to the Rector Chemical Company.

---

[23] The monograph appears in New and Nonofficial Remedies, 1919.

[24] The report of these and subsequent toxicity experiments on procain appeared in the report of the Council on Pharmacy and Chemistry, J. A. M. A. **72**: 136 (Jan. 11) 1919.

TABLE 6

Brand	Date Received	Color	Melting Point, C.*	Ash, %
Procain (Abbott), from Committee on Synthetic Drugs	12/21/17	White	154 –155	None
Procain (Abbott), submitted to Council P. and C.	1/29/18	White	153.5–154.5	None
Procain (Abbott), Gen. Pur. Off. U. S. Army	8/31/18	White	152.5–153.5	None
Procain (Abbott), Gen. Pur. Off. U. S. Army, No. 89999	9/30/18	Slight brownish tint	153 –154.5	None
Procain (Abbott), Gen. Pur. Off. U. S. Army, No. 89998	9/30/18	Slight brownish tint	153 –154.5	0.005
Procain (Abbott), Gen. Pur. Off. U. S. Army, No. 89997	10/ 8/18	Slight brownish tint	153 –154	None
Procain (Abbott), Gen. Pur. Off. U. S. Army, No. 89996	11/ 4/18	Slight brownish tint	153.5–154.5	None
Procain (Abbott), Gen. Pur Off. U. S. Army, No. 810995	11/ 4/18	Slight brownish tint	153.5–154.5	None
Procain (Calco), from Committee on Synthetic Drugs	2/ 7/18	White	153.5–154.5	None
Procain (Farbwerke - Hoechst Co.), submitted to Council	10/24/18	White	153 –154	None
Procain (Farbwerke - Hoechst Co.), submitted to Council	12/10/17	White	153 –154.5	None
Procain (Farbwerke - Hoechst Co.), submitted to Council, market spec. "A 56"	8/ 9/18	White	153.5–154.5	None
Procain (Farbwerke - Hoechst Co.), submitted to Council, market spec. "A 57"	9/ 9/18	White	153.5–154.5	None
Procain (H. A. Metz Lab.), market spec. "A 63"	8/23/18	White	153 –154	None
Procain (H. A. Metz Lab.), market spec. "A 67"	9/23/18	White	153 –154	None
Procain (Rector), from Committee on Synthetic Drugs	12/18/17	White	153 –154.5	None
Procain (Rector), from Committee on Synthetic Drugs	5/ 2/18	White	152.5–153	None
Procain (Rector), market spec.	8/20/18	Slight brownish tint	153 –155	None
Procain (Rector), market spec.	8/23/18	Slight brownish tint	153 –155	None
Procain (Rector), market spec.	8/23/18	Slight brownish tint	153 –154.5	None

---

* U. S. Patent 812,554 — the novocain patent — declares that the salt melts at 156 C. Evidently based on this, both the German Pharmacopeia and past editions of New and Nonofficial Remedies give this melting point. Two specimens of German-made novocain obtained from our files, stated to be manufactured by Farbwerke-Hoechst vorm. Meister, Lucius and Bruening, Hoechst a. M., were found to melt, respectively, between 154 and 155 C. and between 153.5 and 154.5 C. when the melting point was determined according to the direction of the U. S. Pharmacopeia, ninth revision. The various specimens examined at that time melted between 153 and 155 C., and it was decided to permit this range.

Subsequently the products of the licensed firms were submitted to the Council on Pharmacy and Chemistry, which in turn invoked the aid of the A. M. A. Chemical Laboratory and the Cornell University Pharmacologic Laboratory. Later the Council asked the laboratory to examine the *market* supply. Altogether, therefore, a number of products were examined which were found to respond satisfactorily to the tests outlined (Table 6).

An examination of some American-made procain-suprarenin tablets was also made. The procain was determined by liberation of the alkaloid with ammonia water, extraction with chloroform, evaporation of the chloroform, dissolving the alkaloid in one hundredth normal sulphuric acid solution and titrating excess acid with one hundredth normal sodium hydroxid solution. The epinephrin was determined according to the method employed by Seidell,[25] with slight modifications. The tablets contained the claimed amounts of ingredients.

THE SYNTHETIC DRUG SITUATION

Before the war, the American physician was literally bombarded with new and wonderful (?) coal-tar synthetics, most of which were originated in Germany. In fact it seemed that if a by-product in the manufacture of dyes could not be used for a dye per se, then a place might be found for it in the ever increasing lists of medicaments. By clever advertising and propaganda among physicians, an artificial stimulation for coal-tar drugs was created which evidently yielded lucrative financial returns. As a result of the war, it is interesting to observe that of all the synthetic drugs imported into this country from Germany and on which the American patents were controlled by the Germans (up to the time of our entrance into the war), the demand was really sufficient enough to warrant the commercial manufacture of only four of them by American firms. Of couse, a larger number of *nonpatented drugs,* also imported from Germany, are now being made in sufficient quantities in this country; many of the drugs in this class were never patented or are the ones which have survived after the patent had expired, such as acetanilid, acetphenetidin, and acetylsalicylic acid.

In view of the agitation to found an institute for cooperative research as an aid to the American drug industry under the auspices of the American Chemical Society, it will be well for the medical profession to be on its guard against too enthusiastic propaganda on the part of those engaged in the laudable enterprise of promoting American chemical industry. Unless it is, it may be inflicted in the future, as in the past, with a large number of drugs that are either useless, harmful or unessential modifications of well-known pharmaceuticals. It will be well also for the chemists—those engaged in this enterprise—to be sure that the product is of therapeutic value before asking its use as a medicine. The American medical profession has learned that relatively few of the many German synthetics were really valuable or decided improvements over established drugs. If American chemists desire to retain their prestige with the medical profession, they should earnestly endeavor to see that the advantages derived from the war and from such an institute as proposed are not abused in the worthy desire to popularize chemistry both educationally and commercially. They should realize that physicians are in no receptive mood for a flood of synthetics, even though "American-made."

---

[25] Seidell: J. Biol. Chem. **14**: 19, 1913.

On the other hand, the constructive possibilities of chemistry in the service of medicine should serve as a stimulus for American research. Notwithstanding all the pharmaceutical shrubbery which Germany sent to us, still it did contain some synthetics that were worth while. As therapeutics has been benefited by these organic chemicals, it is logical to reason by analogy that there remain other synthetics to be discovered which will occupy places of equal distinction in the modern materia medica. For example, vaccines are of undoubted merit in the field of immunology, but their action is, in the end, chemical; as soon as chemical technic is refined by medicochemical research, it is quite possible that a definite chemical agent (synthetic) will supersede the indefinite bacterial vaccine. Obviously the American chemist has the opportunity of showing his resourcefulness in aiding the public health of America and the world. In this connection, a cooperative institute devoted to purely scientific drug research, and governed in such a manner as to inspire confidence in its humanitarism and unbiased judgment, should serve a most commendable purpose. The hopes of American men of science are for a monumental research institution—cooperative with all the allied professions—and, as the *Chicago Chemical Bulletin* stated, "Stripped of all professional or commercial pettishness and not dominated by any one group of scientists."[26]

---

[26] Proposed Institute for Drug Research, editorial Chicago Chem. Bull., April, 1919, p. 67.

CONCLUSIONS

As for the results of the work so far, they can be summed up in two sentences.

1. American chemists are producing synthetic drugs formerly controlled by Germany, and thus have declared their independence of German chemicals.

2. Judging from the evidence at hand, we can feel assured that the quality of American synthetics will be second to none.

IODIN IN LIQUID PETROLATUM

A. H. Clark, Ph.G., Sc.B.

(Reprinted from The Journal of the American Pharmaceutical Association, August, 1919, p. 611)

Of all the things used in medicine nothing seems to have attracted the attention of all classes of users as has iodin. Perhaps more romantic schemes for the cure of all the ills which afflict mankind have centered in iodin therapy than in any other one drug. Iodin is being used in every conceivable way from crystals to colloid; in vapor; combined as iodid, iodate and the like; organic, inorganic, simple and complex; internal, external and by injection, and yet there seems to be no end to the ingenious schemes for its exploitation.

One of these schemes, and one so simple that it seems at first sight to be hardly worth serious consideration, is that of a solution of iodin in liquid petrolatum. Solutions of this kind have frequently been offered to physicians and the laity. The thing of particular interest is the claim made as to the per centage of free iodin. Five per cent. is frequently claimed. Examination of some of these products in the Chemical Laboratory of the A. M. A.[1] revealed the fact that they did not contain the claimed amount of free iodin. These questions at once arose: Was the low free iodin content due to intentional fraud, the result of carelessness, or of ignorance? Was it impossible to prepare a solution containing 5 per cent., or did the iodin slowly combine with the oil and disappear?

Several years ago the A. M. A. Chemical Laboratory[2] conducted some experiments on the solubility of iodin in liquid petrolatum, which indicated that a saturated solution would contain about 1.4 per cent. These experiments did not show conclusively that no iodin was absorbed by the petrolatum during the process of solution. For this reason, further experiments were conducted with the view of determining both the solubility in and the extent to which iodin is absorbed (disappears as free iodin), if at all, by liquid petrolatums of various kinds. Theoretically such hydrocarbons should not absorb iodin. The results of these experiments are here given.

---

[1] Annual Rep. of the Chem. Lab. A. M. A., 1915, p. 206; Ibid., 1917, p. 87.

[2] Ibid., 1917, p. 87.

A sample of iodin was prepared by sublimation from a mixture with potassium iodid. This sample when dried over sulphuric acid assayed 99.98 per cent. of iodin. Portions of this sample were used in all of the subsequent experiments. To prepare solutions of definite concentrations, in all cases expressed as per centage by weight, an accurately weighed quantity of iodin was placed in a glass-stoppered bottle and an accurately weighed quantity of liquid petrolatum added. The mixture was subjected to treatment as indicated in the various experiments and from the weights of iodin and petrolatum used the per centage of iodin was calculated.

The method of assay employed was as follows: A weighed quantity of the iodin solution was transferred to a bottle or flask by means of several small amounts of chloroform, about 50 c.c. in all. To this was added about 25 c.c. of potassium iodid solution. The mixture was then titrated with tenth-normal sodium thiosulphate until on thorough shaking no iodin passed into the aqueous layer.

To 2.1248 gm. of iodin was added 199.3 gm. of liquid petrolatum. The mixture was shaken frequently each day and after forty days there seemed to be still a few particles of iodin undissolved. The supernatant solution was assayed, however, and found to contain 1.038 per cent. of iodin. The iodin added was 1.055 per cent. Six months later 1.025 per cent. of iodin was found.

To 5.1832 gm. of iodin was added 199.5 gm. of liquid petrolatum. The mixture was heated to 100 C. for four hours with frequent shaking. The iodin was in perfect solution. The per cent. of iodin would then be 4.95. Upon cooling, iodin in abundance crystallized out. After standing a few hours, with frequent shaking, the iodin in solution was determined. This was found to be 1.425 per cent.

These two experiments indicate: First, that the previous findings of the A. M. A. Chemical Laboratory are correct in that only about 1.4 per cent. of free iodin is retained in solution in liquid petrolatum at room temperature. Second, that the quantity of iodin absorbed by liquid petrolatum at room temperature, in seven months at least, is practically none. Third, that iodin dissolves rather slowly in liquid petrolatum at room temperature.

In the experiments, the results of which are tabulated below, the iodin and liquid petrolatum were heated at 100 C. for about four hours, shaking frequently to hasten solution. After cooling, the specimens were assayed and were again assayed at intervals as indicated in the table.

Kind of Liquid Petrolatum Used	Date of Manufacture and First Assay	Weight		Per Cent. Iodin Used	Per Cent. Iodin Found	Per Cent. Iodin Nov. 17, 1918	Per† Cent. Iodin Nov. 19, 1919
		Iodin	Petrolatum				
Stanolind	10/17/18	2.089	188.4	1.096	1.085	1.068	1.067
Squibb	10/14/18	1.9569	186.78	1.0306	1.0232	1.013	1.009
Unknown, bulk*	10/28/18	1.9497	158.2	1.225	1.133	1.075	1.095
Parke, Davis & Co.	10/24/18	2.0869	167.43	1.241	1.2488	1.191	1.180

* Considerable dark sediment formed in this sample during the heating process.

† It should be pointed out here that while every sample showed some absorption, the amount, with the exception of the unknown bulk, is so small that it might even be accounted for on the basis of "experimental error." Every ordinary precaution was taken to insure accuracy, but since about 15 gm. of the solution was used for each determination, it is seen that an error of 0.3 c.c. in the titration would indicate a greater absorption of iodin than that noted.

Conclusions: These experiments show: A solution of iodin in liquid petrolatum is saturated when it contains about 1.4 per cent. of iodin. The amount of iodin absorbed (disappearing as free iodin) by liquid petrolatum, when in contact at room temperature for as long as seven months, or in contact at 100 C. for four hours, or both, is relatively insignificant. Also all the absorption seems to take place during the heating and in the first month of contact.

A NOTE ON A VERY OLD SPECIMEN OF PEPSIN

L. E. Warren, Ph.C., B.S.

(*Reprinted from the Journal of the American Pharmaceutical Association, October, 1919, p. 734*)

An occasion recently arose to examine some rather old pharmaceutical preparations that, it was claimed, contained pepsin. Since the specimens were of unknown age (but known to be at least nine years old) the question arose as to the proper method to be used for making the test for proteolytic power. Since it was not the object of these tests to determine whether the preparations contained pepsin conforming to the present U. S. P. standards, and as the laboratory constant temperature bath was in use for other experiments at 40 C. and was to be so employed for a long period, it was decided to use this temperature according to the method prescribed by the U. S. Pharmacopoeia of 1890 for the valuation of pepsin. In brief, the method consists in digesting 10 gm. of moist egg albumin for six hours at a temperature of from 38 to 40 C. with 100 c.c. of 0.2 per cent. hydrochloric acid which contains 0.0035 gm. of pepsin.

As some of the preparations to be tested (tablets) had been in the laboratory for a number of years the question of the stability of pepsin had to be considered. It chanced that a very old specimen of pepsin and another which had been received ten years before the experiment were in stock. It seemed worth while to compare the proteolytic activity of the two old specimens with a specimen of pepsin of recent purchase, using the assay method outlined above as employed on the other pepsin preparations.

The history of the old specimen was not positively established but it is believed to have been prepared by Mr. F. S. Hereth. The label bore the statement that it had been prepared during the months of October and November, 1880. Consequently, at the time of this test (July), its age was probably nearly thirty-nine years. Unfortunately its initial proteolytic strength was not known, but since the methods for preparing pepsin were not so refined four decades ago as now, it is probable that the specimen was not of 1 to 3,000 value as is now required by the standards of the U. S. Pharmacopoeia. So far as the evidence could be ascertained, the specimen had been stored in a small, cork-stoppered, green-glass bottle at the temperature of the laboratory since the date of manufacture and the container had not often been opened. The other specimen was Armour's so-called insoluble pepsin, which had been received from the manufacturers in July, 1909. Since its receipt it had been stored in its original container, a cork-stoppered bottle of amber glass, at the temperature of the laboratory. The bottle had been opened from time to time and about four fifths of the contents had been used. At the time of sending the preparation, the manufacturer stated that it possessed a strength of 1-3000. The proteolytic strength was not verified at the time of the receipt of the specimen. The specimen used for comparison tests was Armour's "spongy granular, soluble" pepsin received from the manufacturer in May, 1919. The label claimed a strength of 1-3,000 for the preparation.

The old laboratory specimen was a fine, cream-colored powder which was not noticeably hygroscopic. Its odor was not unpleasant, being similar to that of the specimen of recent purchase. Its taste was distinctly saline and somewhat bitter. The material was soluble in water, yielding a turbid solution which was strongly acid toward litmus paper. The ten-year-old specimen was a grayish, somewhat lumpy powder. Its odor and taste were normal. The modern specimen was in the form of pale yellowish scales or granules.

Ash was determined by igniting a weighed quantity in a porcelain crucible, moistening the charred mass with a little ammonium nitrate solution, drying and again igniting. The very old specimen gave 48.8 per cent. of ash while the two more recent specimens gave, respectively, 4.14 per cent. and 3.01 per cent. of ash. As an average of several trials the proteolytic strength of the three specimens was found to be, respectively, 1-500, 1-2,500 and 1-3,000.

An examination was made to determine whether the literature contained reports of examinations of pepsin as old as the oldest specimen here studied, but no records were found. That a specimen nearly thirty-nine years old should retain any proteolytic activity is considered worthy of record.

NATURE'S REMEDY TABLETS

A. H. Clark, Ph.G., B.S.

(Reprinted in part, with additions, from The Journal A. M. A., March 15, 1919, p. 815)

"Nature's Remedy" is manufactured by A. H. Lewis Medicine Co., St. Louis. It is sold in 25 cent, 50 cent, and $1.00 packages. Three of the largest size packages were purchased on the open market and examined in the Association's Chemical Laboratory. Nature's Remedy comes in a tin box, containing an advertising circular, a guarantee blank, and 180 tablets. The advertising circular states that Nature's Remedy is a vegetable preparation which "acts on the stomach, liver, kidneys, and bowels," that it contains no digestives, but that its "purpose in dyspepsia, indigestion, bad breath, loss of appetite, sick headache, and rheumatism is to increase the elimination and keep the intestinal tract clean." The greater part of the circular is devoted to the exploitation of other nostrums of the A. H. Lewis Medicine Co.—"nerve pills," a liniment, headache tablets, and "Sans-Pareil" an "emmenagogue and uterine tonic." The list of diseases and indications for which these alleged remedies are recommended in this circular, numbers about fifty.

A booklet issued by the A. H. Lewis Medicine Co. gives a "formula"(?) for Nature's Remedy. It is stated that there are ten ingredients entering into its composition. The manufacturers generously name seven of these ingredients and admit that "were it not for the vast number of imitators who are ever ready to prey upon the business of established firms and the public we would gladly print the entire formula, for we are even more proud of the three unnamed than we are of the ones given."

The seven ingredients are Burdock, Juniper, Sarsaparilla, Mandrake, Rhubarb, Dandelion and Prickly Ash. There was so little about these to make one share the feeling of pride expressed by the exploiters that diligent search was made for the unnamed three on the chance that something worthy of mention might be found. Chemical analysis showed the presence of aloes, and traces of some alkaloidal drug. The tablets had the characteristic odor of aloes. Extracted with diluted alcohol, an extract representing 61.2 per cent. of the tablet material was obtained. Extracted successively with ether, chloroform, and alcohol, a total of 63.6 per cent. of extractive was obtained. Extracted with water, an extractive representing 50 per cent. was obtained. In every case the extractive resembled aloes in color, odor, and taste and gave the characteristic borax color reaction for aloes described in the U. S. Pharmacopeia.

Since this examination accounted for but one of the mysterious trio of drugs, it was decided to make a microscopic examination, and the aid of E. N. Gathercoal, Instructo in Pharmacognosy in the University of Illinois School of Pharmacy, was sought. The microscopic examination confirmed the chemical findings as to aloes, and also established the presence of powdered cascara sagrada in abundance. Evidence of belladonna root in small quantities was also found and, since the chemical examination showed traces of an alkaloidal drug present, it is possible that the third mysterious stranger is belladonna root. The microscopist's report further stated that rhubarb, as well as all of the other seven named drugs, if present at all, are there in such small quantities that no evidence of their presence could be seen.

A little consideration of the dosage of the drugs mentioned in connection with Nature's Remedy shows clearly the absurdity of such a shotgun mixture, assuming that the drugs mentioned are really present. A table will better convey the idea. The doses given are taken from the U. S. P., N. F., or U. S. Dispensatory, and are average doses:

	Average Dose of the Drug in Grains	Assuming the Drugs Present as Extracts, the Dose, in Grains, Would Be About
Burdock	30	6
Juniper berries	60	12
Sarsaparilla	30	6
Mandrake	5	1 (podophylin $^1/_6$)
Rhubarb	15	5
Dandelion	150	30
Prickly ash	30	6
Aloes	4	2 (aloin ¼)
Cascara	15	3
Belladonna root	1	⅕
	340	71

A tablet containing a single average dose of each of the above drugs would weigh 340 grains if the drugs are simply powdered—as they are claimed to be in Nature's Remedy. If they are represented by their extracts the tablet would still weigh about 70 grains. Yet each Nature's Remedy tablet weighs but 5 grains, of which only 3 grains is medicament! Of course, we should not expect a full dose of each of the drugs, and since there are ten of them, let us say that $^1/_{10}$ of a dose of each should be present. The tablets should still weigh 34 grains, if powdered drugs are present, and about 7 grains if the extracts are used. Since the seven named by the manufacturers are either not present at all or only in very small amounts, our consideration of dosage can be confined to aloes, cascara, belladonna root, and mandrake. Since the microscopic examination showed Nature's Remedy to be largely powdered cascara, the cathartic effect must be due to some very powerful drug since the tablets contain only about 3 grains of medicament. The dose of aloes is 4 grains or more, therefore there is scarcely room for even a moderate dose of aloes along with the cascara, unless it be present as aloin. Thus we cannot account for the active cathartic effect without assuming the presence of some powerful drug like resin of podophyllum or aloin.

Nature's Remedy then is, essentially, aloes or aloin, cascara, and belladonna with, probably, resin of podophyllum. This is such a common cathartic mixture that pills or tablets containing essentially the same ingredients can be purchased in almost any drug store. The manufacturers of these tablets direct the purchaser to take one every night for a week.

They very kindly allow the sufferer (from the effect of the tablets) a few days to recuperate and then suggest that the week of torment be repeated and, if this be survived, another few days of rest is allowed before another round of torture and so on "until the bowels become strong enough to do their work." The ill effects of such violent treatment have been enlarged upon so often by physicians that it is pernicious to suggest that such a course of treatment be followed.

Details of Analysis

Nature's Remedy tablets were uncoated, of a yellow color, and had a decided odor of aloes. Each tablet was stamped with the monogram NR and their average weight was 0.321 gm. or 5 grains. The tablets from two boxes of the tablets were powdered, the powder thoroughly mixed and this mixture was used for examination.

Ash.—Two gm. on incineration left a residue of 0.073 gm. or 3.65 per cent. This was largely aluminum and calcium compounds.

Moisture.—On heating to constant weight at 100 C., 1.201 gm. lost 0.0625 gm. or 5.21 per cent.

Emodin.—Emodin-bearing drugs were found by the usual Bornträger method. Also this test when applied as modified by the U. S. P. in the test for aloes gave the reactions described.

Aloes.—Nitric acid added to an aqueous solution gave a red color at once; alkalies also gave a deep red color; ferric chlorid an olive green; and borax the typical greenish fluorescence. All these color reactions indicate aloes.

Extractive.—Five gm. of the powdered tablets when extracted with ether in a Soxhlet apparatus for five hours gave 0.3908 gm. extractive or 7.8 per cent. On further extraction with chloroform, 0.2968 gm., or 5.94 per cent., extract was obtained, and on still further extraction with alcohol, 2.4938 gm., or 49.87 per cent., extract were obtained. A total extractive amounting to 63.61 was thus obtained. The extracted residue was odorless and tasteless, and a microscopic examination showed vegetable tissue and starch.

One gm. of the powdered tablets macerated over night with dilute alcohol and then percolated with dilute alcohol until exhausted, gave 0.612 gm. of extractive, or 61.2 per cent.

Metals.—Five gm. of the powdered tablets were completely oxidized with potassium chlorate and hydrochloric acid and the solution obtained was saturated with hydrogen sulphid. No sulphids of heavy metals were obtained even after making the solution alkaline with ammonia.

Alkaloids.—Ten gm. of the powdered tablets were examined for alkaloids by the method given under sulpherb tablets (Lab. Rep. A. M. A., vol. 11, p. 48, 1911). Distinct reactions for alkaloid were obtained with Mayer's reagent, iodin, potassium bismuth iodid and phosphomolybdic acid.

Microscopic Examination.—A sample was pulverized; the examination under the microscope showed:

(1) Aloes, indicated by yellowish or reddish-yellow fragments when the powder is mounted in sweet almond oil. These fragments take on an intense red color upon the addition of ammonia water to the mount and dissolve in the ammonia water which acquires a reddish or reddish-yellow color.

(2) Cascara Sagrada—present in abundance as evidenced by numerous fragments of bast bundles bearing crystal fibers and occasional stone cells single or in small groups characteristic of cascara. These tissues, along with parenchyma masses containing small starch grains and rosette crystals, when mounted in sweet almond oil and treated with ammonia water acquired a reddish color which passed but slowly into the ammonia water.

(3) Belladonna Root—Some evidence in the form of fragments of tracheal tubes characteristic of belladonna root was found. If this drug be present it is in small quantity.

(4) Rhubarb, if present, is in very small amount for none of the characteristic rosette crystals, or starch or tracheal tubes could be found.

(5) The other drugs listed as constituents of these tablets could not be identified in the powder and if present are in very small amount.

PART II

REPORTS ABSTRACTED FROM THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION, AND FROM THE ANNUAL REPORTS OF THE COUNCIL ON PHARMACY AND CHEMISTRY

CERELENE

(Abstracted from The Journal A. M. A., Feb. 15, 1919, p. 513)

Cerelene, a paraffin preparation for the treatment of burns, was submitted to the Council by the Holliday Laboratories, with the statement that it was composed of 84 per cent. paraffin, 15 per cent. myricyl palmitate, and 1 per cent. purified elemi gum to which is added oil of eucalyptus 2 per cent. and betanaphthol 0.25 per cent. It was explained:

> "Myricyl Palmitate is a purified form of Beeswax, free from all impurities, acids, etc., which is solely manufactured by this Company. . ."

It was also stated that on "special order" Cerelene has been made containing oil of eucalyptus and resorcin, oil of eucalyptus and picric acid, and picric acid alone. The following report on the preparation was presented to the Council by the referee to whom Cerelene had been assigned:

Cerelene is another compound wax for the treatment of burns. According to the work of Sollmann (J. A. M. A., 1917, 68, p. 1799) it is highly improbable that compound mixtures have any advantage over simple paraffin of low melting point. Cerelene must therefore be considered as an unessential modification of paraffin, and as in conflict with Rule 10, unless definite evidence of superiority be submitted. Cerelene mixtures containing medicinal ingredients also appear unscientific since the evidence that the ingredients do not leave the wax has not been successfully contradicted. Finally, the claims made for Cerelene are rather extreme, and would need some revision before they could be accepted.

The A. M. A. Chemical Laboratory reports:

> The physical properties of Cerelene are as follows:
>
> | | |
> |---|---|
> | Melting point by U. S. P. method | 50.0 C. |
> | Ductility limit | 30.5 C. |
> | Plasticity limit | 26.4 C. |
> | Not strong at | 38.0 C. |
>
> Adheres moderately well; detaches with "pulling." On heating, readily loses eucalyptol, and a small amount of resinous substance forms in the bottom of the beaker. If Cerelene be heated to 145 C. and cooled, the resulting product no longer has the properties of the original Cerelene.[1]

After two years' delay on the part of the manufacturer, the Council authorized publication declaring Cerelene inadmissible for New and Nonofficial Remedies because its superiority over single paraffins had not been demonstrated and the unwarranted claims had not been abandoned.

DEPILAGIENE

(Abstracted from The Journal A. M. A., March 8, 1919, p. 746)

"Depilagiene," or, to give full title, "Franco-American Hygienic Depilagiene," is one of a large number of toilet preparations put on the market by the Franco-American Company of Chicago. In a booklet issued by the Franco-American Hygienic Company, we read that "Depilagiene is an objectionable hair remover," which seems to be the concern's way of saying that it is a remover of objectionable hair. An original bottle of Depilagiene was submitted to the Laboratory for examination:

"The bottle of Depilagiene contained 18.5 grams of a pink powder having an odor resembling that of oil of citronella. Qualitative tests showed the presence of barium, sulphur, sulphid, sulphate, and small amounts of aluminum and calcium; aromatic oils and a red dye were also present. Essentially, the product is a mixture of barium sulphate, barium sulphid, sulphur and starch. A quantitative investigation of the active ingredient, barium sulphid, was made, and disclosed the presence of 22.6 per cent of this drug. As commercial barium sulphid contains only about 50 per cent. of the pure chemical, Depilagiene probably contains approximately 45 per cent. of the commercial drug."

---

[1] The methods of estimating the properties of "Paraffin for Films" were discussed in the 1917 Report of the A. M. A. Chemical Laboratory, Vol. 10, p. 20.

The Journal concluded: It will thus be seen that Depilagiene has no claims to originality, as practically all the chemical "hair removers" are composed of some form of sulphid. Naturally, the preparation is likely to cause more or less irritation of the skin, the amount depending to some extent on the way in which it is used, and to an even greater extent on the tolerance of the individual skin. Like all chemical depilatories, the use of Depilagiene must make the hair coarse.

CUPRASE

(Abstracted, with additions, from The Journal A. M. A., April 12, 1919, p. 1095)

"Cuprase" is a European proprietary, sold in the United States by the Anglo-French Drug Co., Ltd., the firm which also markets it in England. The Council on Pharmacy and Chemistry investigated this product and invoked the aid of the Chemical Laboratory.

"Cuprase" is said to be "prepared in the Laboratories of F. Ducatte, 8 Place de la Madeleine, Paris." According to an advertising circular entitled "The Medical Treatment of Cancer," "Cuprase" is "chemical colloidal copper"; in another place it is "a colloidal copper hydroxid," which is said to be obtained chemically by the reduction of salts of copper in the presence of albumosic acid.

A box (price $8.50 less 10 per cent. discount) of "Cuprase-Doctor Gaube du Gers" was purchased recently from the Anglo-French Drug Co., Ltd.; it contained eight ampules. No information of composition was given on the box, except the line: "Chaque ampoule contient: 0 gr. .00121 de Cuivre pur" (Each ampule contains 0.00121 gm. of pure copper). Each ampule contained approximately 6 c.c. (the label states 5 c.c.) of a brownish, fluorescent liquid which gave the Tyndall cone phenomonon (characteristic of colloidal systems) but did not possess the Brownian movements. Copper was present and also proteins giving the general reaction of albuminoses. Sodium chlorid had been added, very likely in an endeavor to produce an isotonic solution. The amount of solids per ampule approximated 0.13 gm., while the amount of ash was 0.016 gm. The average amount of copper found in two ampules was 0.0025 gm.; another two ampules yielded an average of 0.0051 gm. of copper per ampule. The amount of sodium chlorid, calculated from the sodium present averaged 0.066 gm. per ampule (about 1 per cent.)).

In summing up its report, the Council stated:

> "The available evidence published by the manufacturers and agents presents only vague generalities, and no definite data. The evidence gathered by Weil himself permits an estimate of the value of Cuprase and it is entirely unfavorable. He states (J. A. M. A., April, 1915, p. 1228):
>
> "'Colloidal copper has been used in recent time for the same purpose by Gaube du Gers and by others. I have recently examined the effects of colloidal copper on malignant tumors in man, and have been unable to find that it has any therapeutic value. Furthermore, a study of the distribution of the copper in tumors obtained at operation or by necropsy from individuals so treated failed to show that the copper had been deposited therein.'
>
> "In view of the extravagant and cruelly misleading therapeutic claims, and the indefinite statements of composition, the Council voted Cuprase ineligible to N. N. R., and authorized the publication of this report."

COLLOSOL COCAINE

(Abstracted, with additions, from The Journal A. M. A., April 12, 1919, p. 1095)

"Collosol Cocaine" was submitted to the Council on Pharmacy and Chemistry in October, 1918, by the Anglo-French Drug Co., Ltd., New York, under the claim that it was an "absolute colloid" and that it contained "1 per cent. cocain." The label on the submitted specimen declares:

> "Collosol Cocaine 1-100"
>
> ". . . the Cocaine exists as the pure alkaloid in the Colloidal state—the condition in which it is isomorphic with the protein of the body fluids. The effect is more prolonged than that of a molecular Cocaine Solution and being *non-toxic* absorption presents no practical danger."

The Chemical Laboratory was asked to confirm these statements as far as possible.

Simpson, Hewlett, and Eyre (*Lancet*, April 28, 1917, p. 660) reported "Collosol Cocaine" to be much less toxic than cocain. These writers, however, did not verify the statements as to composition and in the light of subsequent chemical examination it is not to be wondered at that "Collosol Cocaine 1.0 per cent." was much less toxic than a solution containing 1.0 per cent. of cocain hydrochlorid.

Barger, Dale and Durham report from the Department of Biochemistry and Pharmacology, Medical Research Committee (*Lancet*, Dec. 1, 1917, p. 825), that they examined "Collosol Cocaine" and found it to contain but 0.25 per cent. of cocain. They also found that the cocain was not present in a colloidal form. Discussing the low toxicity claimed by the manufacturers, these investigators state:

> "In the samples which we examined the toxicity was, indeed, much lower than that of an ordinary 1 per cent. solution of a cocain salt; but the local anesthetic action was low to a corresponding degree, and both actions correspond satisfactorily with the proportion of cocain chemically recoverable from the solution."

Stroud, of the Crookes Laboratory (which manufactures the preparation), who apparently had been informed of this work in advance of publication, admits the correctness of it, and states (*British Medical Journal*, Nov. 24, 1918, p. 710) that "whilst the colloidal protective apparently absorbs a portion of the cocain, the remainder is found not to exhibit the attributes of a colloid. . . ."

The specimen of "Collosol Cocaine" submitted to the Council and labeled "Collosol Cocaine 1-100" was found to contain at most 0.4 per cent. cocain. The examination was made in accordance with the method used by Barger, Dale and Durham, published in the article referred to above, and calculated as cocain. This method, however, probably would not distinguish between cocain and basic decomposition products, but would include all as cocain in the amount found. The specimen of "Collosol Cocaine" examined was neutral or slightly acid, a fact which tends to confirm the conclusion of the British investigators that "Collosol Cocaine" contains cocain in noncolloidal form and precludes an increased physiologic effect due to alkalinity.

The Council adopted the report of the Laboratory and declared "Collosol Cocaine" inadmissible to New and Nonofficial Remedies.

The quantity of sample submitted did not permit of extended examination and no duplication of work. With all precautions taken to insure complete extraction and accurate weighing, 3 c.c. gave 0.012 gm. residue, dried at 100 C. corresponding to 0.4 per cent. and not 1 per cent. The "Collosol Cocaine" was made alkaline with ammonia, extracted several times with chloroform, the chloroform allowed to evaporate, the residue dried and weighed. The residue gave typical general alkaloidal reactions.

The sample submitted, then, contained but 40 per cent. of the cocain claimed.

LANE'S ASTHMA CURE

(*Abstracted, with additions, from The Journal A. M. A., May 10, 1919, p. 1386*)

In certain cheap weeklies and in some not-too-particular newspapers, one may find advertisements in large black-faced type announcing: "Asthma Cured Before You Pay," in which D. J. Lane, St. Marys, Kan., offers to "send you a $1.25 bottle of Lane's Treatment on free trial." Other advertisements headed either "Discovered *Cure* for Asthma," or "Discovered *Remedy* for Asthma," as the advertising rules of the publication may require, assert that a "Kansas Chemist" has discovered a "simple home remedy for asthma" which has "easily cured" those "who had been suffering from asthma for forty years."

In earlier days, "Lane's Asthma Treatment" used to be "Lane's Asthma Cure," and long after the federal Food and Drugs Act was enacted, which penalizes false claims made on the trade package, the same false claims were made in other advertising paraphernalia—not subject to the law—which Lane used in his mail-order quackery.

One original bottle of "Lane's Treatment Double Strength for Asthma and Hay Fever," sold by D. J. Lane, St. Marys, Kan., was submitted to the chemical laboratory for examination. The bottle contained 150 c.c. (about 5 fluidounces) of a brown liquid, with some suspended matter, having an aromatic odor and a bitter, gentian-like taste. The specific gravity was 1.0471. "Twelve and one-half per cent of alcohol, or less" was declared on the label. Qualitative tests indicated the presence of calcium, iodid, sugar, alcohol, and vegetable extractives. The sugar was present mainly in a form (such as glucose) which directly reduced Fehling's solution, although a small amount of sugar was present which did not reduce Fehling's solution until after inversion with hydrochloric acid (characteristic of sucrose—cane or beet sugar). (A bottle which had been in the A. M. A. files for two years did not give these results, the sugar being present as sucrose). Alkaloidal and emodin-bearing drugs were not present. Quantitative determinations yielded the following:

	Per Cent.
Alcohol, by volume	11.30
Calcium (Ca^{++}), by weight	0.59
Iodin (present as Iodid-I^-), by weight	3.26
Ash, by weight	2.05
Sugar (direct reduction calculated as dextrose), by weight	5.93
Total Sugar (after inversion calculated as dextrose), by weight	6.36

The examination indicated that each 100 c.c. (approximately 3⅓ fluidounces) contained 11.3 c.c. (about four teaspoonfuls) of alcohol, 3.96 gm. (60.8 grains) of anhydrous calcium iodid (CaI_2) and 6.66 gm. (about 102 grains) of sugars, chiefly dextrose.

In commenting on the analysis, THE JOURNAL stated:

"It will be seen by the chemist's report that Lane's 'wonderful discovery for asthma' is essentially a solution of iodids in alcohol and water with vegetable extractives. Each dose of Lane's preparation contains approximately 2.5 grains of calcium iodid. This gives a daily dosage which is equivalent to 11.3 grains of potassium iodid. Iodids, of course, have been used for years by the medical profession in the treatment of certain forms of asthma. Under careful supervision the use of iodids in selected cases of asthma may give satisfactory results. Self-dosing with iodids, however, especially in cases in which the conditions may or may not indicate this drug, is by no means free from danger. Long continued use or overdosing may bring about symptoms of iodism with edematous conditions of the larynx that may seriously interfere with respiration, even to the point, occasionally, of necessitating trachetomy and in rare instances, causing death. Even where the symptoms are not so severe there may be skin eruptions, frontal headache, sore throat, neuralgic pains, anemia, etc. It is hardly necessary to say that in the exploitation of Lane's nostrum there is no warning of such danger."

Details of Analysis

Alcohol.—The alcohol was distilled from 50 c.c. of the original (to which about 80 c.c. of water had been added) and the distillate was made up to exactly 100 c.c. The specific gravity of the distillate at 15.6 C. was 0.99196. This is equivalent to 11.30 per cent. of alcohol by volume in the original.

Calcium.—Ten c.c. of the original was diluted with water and the calcium precipitated as calcium oxalate. This was filtered, washed, dried and carefully heated until a constant weight of calcium carbonate was obtained. (A) Ten c.c. yielded 0.1598 gm. of calcium carbonate ($CaCO_3$) equivalent to 0.064 gm. of calcium (Ca^{++}). (B) Ten c.c. yielded 0.1488 gm. of calcium carbonate ($CaCO_3$) equivalent to 0.059 gm. of calcium. The two determinations gave an average of 0.61 gm. of calcium (Ca^{++}) in 100 c.c., equivalent to 0.59 per cent. by weight.

Iodid.—Twenty-five c.c. of the original was diluted to 250 c.c. and $^{1}/_{10}$ aliquot part (25 c.c.) was used for the iodid determinations. The iodid was precipitated by addition of silver nitrate in the presence of nitric acid. (The absence of all but faint traces of chlorid and bromid had been demonstrated.) (A) Twenty-five c.c. of the diluted specimen yielded 0.1594 gm. of silver iodid, equivalent to 3.44 gm. of iodin in the form of iodid (I^-) in 100 c.c. (B) Twenty-five c.c. of the diluted specimen yielded 0.157 gm. of silver iodid, equivalent to 3.40 gm. of iodin in the form of iodid (I^-). The average of these determinations is 3.42 gm. in 100 c.c., which is equivalent to 3.26 per cent. of iodin [present as iodid (I^-)] by weight. This percentage of iodid is equivalent to 0.54 per cent. calcium (Ca^{++}), which agrees closely with the amount of calcium found to be present.

THE DR. D. A. WILLIAMS RHEUMATIC TREATMENT

A Mail-Order "Kidney and Bladder Disease" Cure

(Abstracted, with additions, from The Journal A. M. A., May 31, 1919, p. 1632)

"The Williams Treatment," according to the Dr. D. A. Williams Company, which sells it on the mail-order plan from East Hampton, Conn., "conquers kidney and bladder diseases, rheumatism and all other ailments when due to excessive uric acid." The Dr. D. A. Williams concern is not operated by Dr. D. A. Williams. In fact, so far as our records show, and they are based on official data, D. A. Williams is not an "M.D." The company is practically owned by a man who used to be a traveling salesman, although an attorney also seems to have an interest in this mail-order "kidney cure."

In accordance with the tenets of empiricism, the public, which is asked to pour this nostrum down its throat, is given no hint as to what there is in it. But:

> "The Williams Treatment is different from any Kidney or Bladder remedy on the market. Its ingredients are scientifically blended and of a distinctly curative nature. It does *more* than merely deaden pain and give short relief. It is pure and wholesome and *does not* contain Alcohol, Morphin, Opium, Cocain, Salpeter or Dangerous Drugs.
>
> "It expels Uric Acid, helps to sterilize the urine, cleanses the kidneys and gives tone and strength to their tubular cells. It is a restorative of Kidney Vitality and casts out poisonous matter whether of a toxic nature or not. It cleanses the bladder and quells inflammation of its

mucous surface and its effect on calculus or gravel formation is to aid in their dissolution. It is unequalled in building up weak urinary ducts and glands and a great aid to natural passage of urine."

The Dr. D. A. Williams Company sends, to those who write for it, a free sample, emphasizing that this is but a trial and that the recipient should purchase at least a full-sized bottle, $1.25—"6 bottles for $6.00." A letter, printed to simulate an individual typewritten communication, is also sent, explaining that "Dr. Williams has treated uric acid conditions for more than thirty-six years and he varies the treatment to meet the demands for each different condition." For this reason the prospective purchaser is urged to fill out the symptom blank so that advice "concerning diet and other matters" may be sent.

Several bottles of the Williams Treatment were purchased and submitted to the A. M. A. Chemical Laboratory for examination. Here is what the chemists report:

"The Williams Treatment is a dark reddish brown mixture with the odor of wintergreen or methyl salicylate. It contains considerable undissolved crystals which pass into solution when water is added to the 'treatment.' Acetate, bicarbonate, caramel, potassium, traces of formate and of salicylate were found present. No nitrogenous drugs or alkaloids could be detected. Potassium was the only metal found. Samples vary somewhat in the quantities of the constituents found but are approximately as follows:

"Residue when dried at 100 C. (including undissolved crystals) 57 gm. in 100 c.c.

"Potassium acetate (calculated from total volatile acids) 48 gm. in 100 c.c.

"Potassium bicarbonate 7 gm. in 100 c.c.

"The formate found was in very small amounts and may have been formed from the caramel color during the distillation with acid. The salicylate, also in very small amount, no doubt came from the methyl salicylate or oil of wintergreen.

"From this examination we conclude that Williams Treatment is essentially a mixture containing, in 100 c.c., 48 gm. of potassium acetate in solution and about 7 gm. of potassium bicarbonate, the latter being largely undissolved. The mixture is colored with caramel and flavored with oil of wintergreen or methyl salicylate."

Details of Analysis

Three different lots of the Williams Treatment were examined. The first was a single bottle containing 28 c.c., the second was a single bottle containing 54 c.c., and the third a lot of six bottles each containing 44 cc. The samples were about alike in that they had the odor of methyl salicylate or oil of wintergreen, a dark red-brown color, and contained undissolved crystals.

For the analysis the contents of one bottle (or more in the same proportion) were transferred to a 250 c.c. flask, distilled water being used to aid in the complete transfer. The flask was filled to the mark and shaken thoroughly to dissolve the crystals. In most cases 25 c.c. of this dilution, representing one tenth of the contents of a bottle (including undissolved crystals) were used for each of the various determinations. All the results are expressed in grams per hundred cubic centimeters of the original Williams Treatment.

Total Solids.—This determination was made by evaporating 25 c.c. of the dilutions at first on the steam bath and finally to constant weight at 100 C. in the oven.

Sample No. 1 gave 64.1 gm. of solids in 100 c.c.
Sample No. 2 gave 59.4 gm. of solids in 100 c.c.
Sample No. 3 gave 56.8 gm. of solids in 100 c.c.

Caramel.—All samples responded positively to the Amthor[1] test for caramel.

Sugar.—Williams Treatment reduced Fehling's solution only very slightly, even after heating with acid. The slight reduction may have been due to the caramel.

Methyl Salicylate.—The Treatment had the odor of oil of wintergreen.

Salicylate.—The Treatment was made alkaline with sodium hydroxid and warmed. After cooling and acidulation, it was extracted with chloroform and on evaporation of the chloroform a slight residue was obtained. This residue contained some crystals and a solution in water gave the typical violet color with ferric chlorid.

Alkaloids.—The Treatment was made alkaline with ammonia water and extracted with chloroform. On evaporation of the chloroform very little residue was obtained. This gave no reactions for alkaloids.

Nitrogenous Matter.—When examined by the Kjeldahl method for nitrogen, no nitrogenous matter was found.

Nitrate.—The usual test for nitrate failed to show its presence.

---

[1] Leach: Food Inspection and Analysis, Ed. 3, 1913, p. 752.

Hexamethylenamine.—The fact that no ammonia was found by the Kjeldahl method shows that this substance is absent.

Chlorid, Bromid, Iodid.—The usual tests indicated the absence of these.

Acetate.—With strong sulphuric acid and alcohol the characteristic odor of ethyl acetate was obtained. The distillate from an excess of sulphuric acid was strongly acid in reaction. This distillate when made neutral became deep red with ferric chlorid and this red solution when boiled produced a reddish precipitate.

Bicarbonate.—With hydrochloric acid brisk effervesence took place. Toward phenolphthalein Williams Treatment is not alkaline but on boiling becomes strongly akaline. Some of the undissolved crystals effervesced with acids. The aqueous solution was acid to phenolphthalein but became alkaline on boiling.

Potassium.—The ash was examined in the usual manner for metals. Potassium was the only one that could be detected.

Formate.—The distillate from the acidulated Treatment reduced alkaline silver solution slightly and also mercuric chlorid slightly.

Butyric Acid.—On acidulation a slight odor of butyric acid was noted. No other tests for this substance were made.

QUANTITATIVE

Volatile Acids.—The bicarbonate was removed from 25 c.c. of the dilution by adding a slight excess of barium hydroxid. After filtering off the barium carbonate and washing well, the filtrate was acidulated with phosphoric acid and distilled to a small volume. Water was added and the distillation repeated and this repeated until no acid came over in the distillate. From 25 c.c. of the dilution of Sample No. 2, equivalent to 5.4 c.c. of the Treatment, volatile acids equivalent to 26.13 c.c. of normal potassium hydroxid were obtained. This indicates 2.564 gm. of potassium acetate or 47.5 gm. in 100 c.c. of the Treatment.

In a duplicate, 26.23 c.c. of normal alkali were used, equivalent to 2.5736 gm. of potassium acetate, or 47.7 gm. in 100 c.c. of the Treatment; average 47.6 gm. in 100 c.c.

From 25 c.c. of the dilution of Sample No. 3, equivalent to 4.35 c.c. of the original Treatment, volatile acids equivalent to 18.77 c.c. of normal potassium hydroxid were obtained. This indicates 1.8417 gm. of potassium acetate, or 42.34 gm. in 100 c.c. of the Treatment.

In a duplicate, 18.82 c.c. of normal alkali were used, equivalent to 1.8466 gm. of potassium acetate or 42.45 gm. in 100 c.c. of the Treatment; average 42.4 gm. in 100 c.c.

Bicarbonate.—It was found that a very good end point could be obtained by adding phenolphthalein to the diluted Treatment and titrating the boiling solution with normal acid until permanently colorless.

In this manner, 50 c.c. of the dilution of Sample No. 2, representing 10.8 c.c. of the Treatment, required for neutralization 7.63 c.c. of normal acid. This indicates 0.7638 gm. of potassium bicarbonate or 7.06 gm. in 100 c.c. of the Treatment. A duplicate gave the same result.

A specimen of 50 c.c. of the dilution of Sample No. 3, representing 8.7 c.c. of the Treatment, required for neutralization 5.86 c.c. of normal acid. This indicates 0.5866 gm. of potassium bicarbonate or 6.74 gm. in 100 c.c. of the Treatment.

A duplicate required 5.66 c.c. of normal acid, indicating 0.5666 gm. of potassium bicarbonate or 6.51 gm. in 100 c.c. of the Treatment; average 6.73 gm. in 100 c.c.

Total Alkalinity of Ash.—The total solids from 25 c.c. of the dilution of Sample No. 2, representing 5.4 c.c. of the Treatment, was charred. The charred mass was leached out with hot water and the solution titrated with methyl orange as indicator. The sample taken required 30.72 c.c. of normal hydrochloric acid, indicating 2.1228 gm. of potassium carbonate in the ash. The neutral solution was evaporated and the potassium chlorid dried and weighed. The weight obtained was 2.2975 gm., indicating 2.1302 per cent. of potassium carbonate.

In the same manner the ash from 25 c.c. of the dilution of Sample No. 3, representing 4.35 c.c. of the Treatment, required 21.82 c.c. of normal sulphuric acid, indicating 1.5078 gm. of potassium carbonate. On evaporation this gave 1.9103 gm. of potassium sulphate, indicating 1.5144 gm. of potassium carbonate.

The alkalinity of the ash is then due entirely to potassium bicarbonate.

COLLOSOLS

(Abstracted, with additions, from The Journal A. M. A., June 7, 1919, p. 1694)

Collosol is a name applied to the products of Crooke's Laboratories, London, England, and marketed in the United States by the Anglo-French Drug Co., Ltd., New York. There are a number of Collosols and some are said to be colloidal solutions of metals, some colloidal alkaloids, colloidal iodin, etc.

The Anglo-French Drug Co. submitted several of these to the Council on Pharmacy and Chemistry of the A. M. A. and the laboratory was asked to examine them. With the exception of Collosol Cocain (reported on elsewhere in this volume), the examination was conducted with a view of determining whether or not the products were true colloids in suspension.

An idea of what these products are is obtained from what seems to be an abstract of the original patent for Collosols given in the *Pharmaceutical Journal*, Dec. 7, 1912, p. 718, which is essentially as follows:

> British patent No. 21,521, 1911, colloidal metals and colloidal salts of metals. Henry Crookes, analytical chemist, 109 Ladbroke Grove, London, and Lewis Stroud, solicitor, 268-271 Birbeck Bank Chambers, High Holborn, London. This invention relates to the preparation and formation of solutions of colloidal metals suitable for germicidal purposes. The invention consists in producing colloidal metals from solutions of their salts of the order of about one in one thousand. To 1 quart of distilled water (17,500 grains) add 300 grains of peptone and 800 grains of sodium chloride, and boil until the peptone is completely dissolved. Cool, filter, and make to original volume with distilled water. In another quart of distilled water dissolve 27.59 grains of silver nitrate. Equal quantities of these solutions are mixed. When produced on a large scale, this mixture is allowed to stand for twenty-four hours, then placed in a hot air oven at 100° F. forty-eight hours. Precipitation takes place and the clear supernatant solution is drawn off and constitutes the clear fluorescent silver chloride. For mercury a similar procedure is adopted, but different proportions are used. Other salts may be used as those of thallium, selenium, cobalt, silver, mercury, antimony, arsenic, bismuth, lead, nickel, iron, aluminum, zinc, copper. An alternative method may be used, which con-

sists in boiling the organic salt solution in contact with the particular metal which it is desired to transform into colloidal form. For medical purposes, the colloids produced may be applied either topically, or by injection, or by mouth, but they may also be used for the sterilization of food, drugs, or water.

Further information is gained from two U. S. patents which have been granted to Henry Cookes, A. R. S. M., F. C. S., 109 Ladbroke Grove, London. No. 1,059,841, dated April 22, 1913, relates to the Production of Colloidal Metals. This seems to be, in substance, the same as the British patent abstracted above. No. 1,116,247, dated Nov. 3, 1914, is issued to Henry Crookes and Lewis Stroud and relates to "new and useful improvements in the production of metal colloids." The first improvement consists in simply mixing very dilute solutions of metal with peptone, omitting the sodium chlorid. A further improvement is the addition of 0.1 per cent. of phenol for the purpose of rendering the mixture permanently stable, "experience having shown that some metal colloids under certain conditions not yet fully understood have the tendency to break down after a certain period." The phenol, it is claimed, has a tendency to counteract this decomposition.

From this it seems that the Collosol preparations are claimed to belong to the class of the protected metallic colloids, the protecting colloid being peptone. They may also contain phenol as a protective.

A true colloid should be uniform in composition and show no precipitate.

There were submitted to the Council samples of the following metallic Collosols:

Collosol Argentum
" Arsenicum
" Cuprum
" Ferrum
" Hydrargyrum
" Manganese.

Also Collosols of Iodin and Sulphur, and finally Collosols of Cocain and Quinin, were submitted.

Of all the above, except sulphur, only three small ampules have been submitted. This does not admit of any extended chemical examination, but a statement of the appearance of each is of value.

Collosol Arsenicum, 0.2 per cent.—Very turbid with large quantities of a lemon yellow, flocculent precipitate; on shaking does not become homogenous and rapidly separates again.

Collosol Argentum, 1-2000.—The liquid has a slight opalescence. There is considerable deposit of a heavy, black precipitate; does not become homogenous on shaking and the black substance quickly separates again.

Collosol Cuprum, 0.05 per cent.—Dark red, somewhat opalescent liquid; no precipitate; may be colloidal.

Collosol Ferrum, 1-2000.—Liquid clear; large quantities of dark brown, flocculent precipitate; the precipitate is not distributed evenly when the mixture is shaken and settles out quickly on standing.

Collosol Hydrargyrum, 5 per cent.—Milky liquid; large quantities of white deposit mixed with considerable black; the deposit mixes fairly well but the greater part settles out after standing an hour or two.

Collosol Manganese, 2.5-1000.—Clear reddish brown liquid without deposit of any kind; is not opalescent or fluorescent.

Collosol Iodin, 1-500.—Very pale straw colored liquid without deposit; has a slight opalescence.

Collosol Sulphur, 1-100.—Liquid is opalescent. There is some deposit of yellow particles. A four ounce bottle was also submitted. The liquid in this bottle is milky with considerable deposit of yellow crystals like ordinary sulphur.

Collosol Cocain, 1-100.—Transparent, colorless liquid with no deposit. Chemical examination showed 0.4 per cent. of what might be cocain. This residue gave alkaloidal tests.

Collosol Quinin, 1-100.—Slightly opalescent, colorless liquid with no deposit; gives alkaloidal reactions.

Based on this report, the Council on Pharmacy and Chemistry declared the Collosol preparations ineligible to New and Nonofficial Remedies and reported (The Journal, June 7, 1919, p. 1694):

According to the original patent specifications for Collosols, the metals are precipitated or treated with "peptone," which acts as the suspending or stabilizing agent. The method of using the peptone makes it doubtful, in the first place, whether the major part of the metals is present in colloidal form, or merely in the form of peptonates, i. e., as ordinary salts.

Moreover, the later patents indicate that the products have been unsatisfactory; "experience having shown that some metal colloids under certain conditions not yet fully understood have the tendency to break down after a certain period" (U. S. patent No. 1,116,247). Phenol, it is claimed, has a tendency to counteract this decomposition, and the patent covers the use of phenol for this purpose.

It is difficult to see how phenol could possibly have such action. In fact, it obviously does not, for a number of the samples of Collosols submitted to the Council had separated. For instance, "Collosol Hydrargyrum" was not a colloidal solution at all, but a suspension of a coarse powder. The ampules of "Collosol Ferrum" contained a considerable quantity of flocculent precipitate. If either of these preparations were injected intravenously as directed, death might result, making the physician morally if not legally liable.

The recklessness of the claims is further illustrated by the advice that these indefinite mixtures of poisonous metals can be injected in unlimited quantities. Thus, Henry Crookes stated (Chemical News, May 7, 1914, p. 218) that Collosols "contains so small a proportion of metal, viz., 1 in 2000, that even a poisonous body like arsenic can be used with impunity." He stated that they may be applied as a lotion, or by intramuscular or intravenous injection, and that "one pint or more can be injected intravenously."

In the case of "Collosol Cocain," as was brought out in the Council's report published in THE JOURNAL, April 12, 1919, the manufacturers have admitted that the product is not what they have claimed—and still claim—for it. The report of the A. M. A. Chemical Laboratory showed that "Collosol Cocain," instead of containing 1 per cent. of cocain as claimed, contained, in fact, at most not more than 0.4 per cent. of cocain.

The report of the A. M. A. Chemical Laboratory on the Collosol products was sent by the Council to the New York office of the Anglo-French Drug Co., Ltd., in duplicate, in order to facilitate reference to the London office. This was some months ago. The information which the Council requested has not yet been received, nor has the Anglo-French Drug Co., Ltd., indicated its intention of supplying such information. On the other hand, claims to which specific objection have been made, continue to appear in current advertising.

DR. DE SANCTIS' RHEUMATIC AND GOUT PILLS

(Abstracted from The Journal A. M. A., July 19, 1919. p. 213)

Dr. DeSanctis' Rheumatic and Gout Pills 'are sold by Edward Cleaver, 13 Clerkenwell Road, London, England. The American agents are E. Fougera and Co., Inc., New York. The package is a round pill box and contains twelve pills and a circular, which directs that one pill be taken every eight hours until relieved. In the package there is also a circular advertising Dr. DeSanctis' Gout and Rheumatic Paint, with directions for its use. On the cover of a box, which contained six of the retail packages, is the statement that these pills have been in general use for nearly 100 years, and that their sale has been built up without advertising.

DeSanctis' pills are round, uncoated, and have a light brown color. There was some variation in the color of different lots, one lot in particular being gray rather than brown. A little arrowroot starch was found in each box, this evidently having been used as a dusting powder. The pills were very hard, rather brittle, but quite difficult to powder. The pills were not readily disintegrated by water or diluted acids, even when warmed, but when warmed with a dilute sodium hydroxid solution they readily disintegrated.

Ten pills weighed 3.213 gm., an average of 0.3213 gm., or 5 grains. The arrowroot starch used as a dusting powder was removed as completely as possible by rolling the pills in a cloth. Several dozen pills were then powdered and the powder thus obtained used for the analysis.

A microscopic examination of the powder showed powdered colchicum seed in abundance and also traces of arrowroot starch, no doubt from that used as the dusting powder.

Since colchicum seed was so abundant, the powder was assayed by the U. S. Phamacopoeial method for colchicum seed (U. S. P. IX, p. 120), slightly modified so that less of the powdered pills than directed there could be used. In one assay 3.75 gm. gave 0.0204 gm. of colchicin or 0.54 per cent. In a duplicate, 5 gm. gave 0.0234 gm. of colchicin or 0.47 per cent.; average 0.5 per cent.

The alkaloid obtained had the characteristic appearance and odor of colchicin when separated from the seed under these conditions. The solution in water and acid was yellow; the aqueous solution was intensely bitter, and the yellow color intensified with acids. The dry residue became intensely yellow with concentrated sulphuric acid; with nitric acid it became violet turning to yellow, and with concenrated sulphuric acid and potassium nitrate it gave a yellowish green color, turning to violet and finally to a wine color. All these reactions are typical of colchicin.

From 1 gm. of the powdered pills there was obtained 0.0425 gm. of ash, or 4.25 per cent.

When the powdered pills were extracted with chloroform in a Soxhlet apparatus, a very uniform quantity of extract was obtained. From 5 gm. there was obtained, in one case, 0.581 gm.; in another, 0.5755 gm., and in a third, 0.588 gm., the average being 0.5815 gm. or 11.63 per cent.

On still further extracting with alcohol, a small amount of extractive was obtained, the amount depending on the length of time the extraction was continued.

On extracting with hot water the residue left after exhaustion with chloroform and with alcohol, a further extract was obtained. In one case, it amounted to 0.4763 gm. or 9.53 per cent., and in another case it amounted to 0.470 gm., or 9.40 per cent.; average 9.47 per cent.

In attempting to dry the pills or the above-mentioned chloroformic extract at 100 C., a crystalline sublimate was obtained which had the odor of benzoic acid. The crystals were acid, their neutral solution gave a flesh-colored precipitate with ferric chlorid, and they melted at 120-121 C. This crystalline substance appeared to be benzoic acid.

The quantity of benzoic acid in this extract was determined by heating it to about 140 C. A current of air was drawn through the flask and the sublimed benzoic acid collected in a cooled tube. The benzoic acid was washed out of the tube with neutral alcohol, and the solution was titrated with N/10 potassium hydroxid. In one case, 11.25 c.c. of tenth-normal alkali was used, indicating 0.1373 gm. of benzoic acid; in another, 12.27 c.c., indicating 0.1498 gm. of benzoic acid; average 0.1436 gm., or 2.87 per cent. In a third case the temperature reached 250 C., and there was some decomposition of the fat in the flask and some colored material distilled over. For this sublimate 15.54 c.c. of tenth-normal alkali were required.

After evaporating the alcohol and acidulating the solutions obtained in the previous experiments, the benzoic acid was extracted with chloroform. In the first case, 0.1383 gm. was obtained; in the second, 0.1541 gm.; average 0.1462 gm., or 2.92 per cent. of benzoic acid.

When the original chloroformic extract was heated until all of the benzoic acid had been driven off, the residue had the appearance of a semisolid fat. It compared quite closely in color, odor, etc., with the fatty material obtained by extracting colchicum seed with chloroform, although the odor was more suggestive of oleic or stearic acid. It was distinctly acid, which is also true of the fatty material obtained from a sample of colchicum seed.

The extract obtained with hot water was light yellow; gummy, at first, but dried to a glass-like brittle mass. It had a slight burned-sugar odor and taste, and was neutral in reaction. It was strongly dextrogyrate and at once reduced Fehling's solution as well as alkaline silver nitrate solution. On boiling with potassium hydroxid solution, it turned deep red. It also gave the Molisch carbohydrate reaction, and the ozazone test in seventeen minutes as described in Mulliken (Identification of Pure Organic Compounds, Ed. 1, 1905, p. 26). These are all characteristic reactions of lactose or milk sugar.

From this examination we conclude that DeSanctis' pills contain powdered colchicum seed, benzoic acid, and sugar of milk. There is also present fatty material which resembles the fat of colchicum seed, but may be, in part, added fatty acid. The percentage of colchicin found (0.50) is about that of a good quality of colchicum seed, the U. S. Pharmacopeial standard being not less than 0.45 per cent. Since the pills contain material other than colchicum seed, this assay would indicate a colchicum seed of high alkaloidal content, or the possible reinforcement of the pills with colchicum extract or colchicin.

The amount of benzoic acid, 2.92 per cent., or about 1/7 grain per pill, is insignificant from a therapeutic standpoint, since an average dose is 0.5 gm., or 8 grains. Fatty acids, and the fatty matter from colchicum seed are inert, at least in the quantities found here. The only office which fatty acids might perform, would be to give the pills an enteric quality, preventing their absorption until they reach the intestine. The sugar of milk, about 10 per cent., or ½ grain per pill, no doubt is simply an excipient.

DeSanctis's pills are therefore essentially 5 grain doses of powdered colchicum seed, of which the average dose is 0.2 gm., or 3 grains (U. S. P. IX, p. 120).

THE JOURNAL in presenting the facts contained in the above report made the following comments:

"Here then, we have sold for self-medication an extremely poisonous drug, with no warning of the risk the public runs in using it. While the directions call for "one pill every 8 hours until relieved," it is notorious that the public takes the attitude toward "patent medicines" that, if a little is good, more is better, and the average user of remedies for self-treatment is likely, unless there is some warning, to use his own discretion as to the amount taken.

"The invidual dose is above that of the average recommended in the United States Pharmacopeia. Colchicum or its alkaloids—or for that matter, any drug as toxic as colchicum—have no place in preparations of the home-remedy type. In the case of all "patent medicines," public interest demands that the full quantitative formula of the therapeutically active ingredients should be given on the label, for when the public prescribes for itself, it has a right to know what it is taking. Unfortunately, public interest clashes with vested interests and, as usual, vested interests get the better of it. In the case of such dangerous preparations as DeSanctis' pills, if their sale is to be permitted at all, not only should the names and quantities of all therapeutically active ingredients in the mixture be given, but the law should require that the word POISON be plainly printed on the label."

DR. MILES' HEART TREATMENT

(Abstracted, with additions, from The Journal A. M. A., July 26, 1919, p. 287)

"Dr. Miles' Heart Treatment" is put out by the Miles Medical Co. of Elkhart, Ind. The history of the exploitation of this preparation is fairly typical of the history of "patent medicines" in general. Before the days of the Food and Drugs Act, when there was no penalty for falsifying on the trade package, this preparation was "Dr. Miles' New Cure for the Heart," and the carton bore the legened:

> "DR. MILES' NEW CURE is the Latest and Greatest Discovery for Weak and Diseased Hearts, and the only Safe and Agreeable one known. It is the result of vast experience and years of Scientific investigations by one of the most able and learned physicians of the age."

The trend of the advertising of the "heart cure" can be illustrated by quoting from the descriptive paragraphs in advertising material of various dates:

> "Dr. Miles' New Heart Cure: a wonderful, strengthening medicine for weak heart, permanently curing all diseases of the Heart and Circulation"

This later became:

> "Dr. Mile's Heart Cure, the greatest heart builder and regulator known."

And still later:

> "Dr. Miles' Remedy for the Heart: a strengthening medicine and tonic for the weak heart."

And now is:

> "Dr. Miles' Heart Treatment: a strengthening regulator and tonic for the weak heart."

No information regarding the composition of Dr. Miles' Heart Treatment is vouchsafed by the manufacturers, at least beyond that which the law requires. Thus the labels used since the passage of the Food and Drugs Act admit the presence of 11 per cent. of alcohol. Like other "patent medicine" exploiters the makers of this nostrum wish to retain the element of secrecy probably for the mystery that it throws over their product and for the scope it gives to the imagination of their advertisment writers. Nevertheless they are apparently anxious to capitalize wherever possible any statements regarding the drugs used in their preparation, so that the Miles Medical Company publishes under the heading "What Medical Authorities Say," some quotations relative to two of the alleged ingredients of the nostrum. Some of these quotations are garbled and modifying clauses have been omitted, while in other cases the quotations are from uncritical sources.

Below some of the quotations given by the Miles concern are compared with the original authority:

AS QUOTED BY MILES	THE ORIGINAL QUOTATION
"Those who have used all heart remedies unite in the belief that for breadth of action, for specific directness, for reliability and smoothness and trustworthiness, it takes preference over all the rest. Its influence is admirable where indicated, and it is invaluable in many cases. Other remedies will do as much in single lines, but none will do more, and none will exercise all of its desirable influences."	"Those who have used all heart remedies unite in the belief that for breadth of action, for specific directness, for reliability and smoothness and GENERAL trustworthiness, CACTUS takes preference over all the rest. Its influence is admirable where indicated, and it is invaluable in many cases. Other remedies IN SOME CASES will do as much in single lines, but none will do more, and none will exercise all of its desirable influences." *(From Ellingswood, Materia Medica, Therapeutics, and Pharmacognosy, 1898.)*
"It is especially in functional disorders of the heart that it is most useful; in these cases ,we now rarely prescribe any other cardiac remedy."	"It is especially in functional disorders of the heart that CACTUS is mostly useful; in these cases we now rarely prescribe any other cardiac remedy." *(From P. Watson Williams, "Practitioner," 1891, Vol. 47.)*
"It is of value in nearly all cases of disease where the condition is one in which the heart fails to do its proper amount of work." *(From pamphlet entitled, "What Medical Authorities Say," distributed in Chicago, March, 1919.)*	"DIGITALIS is of value in nearly all cases of CARDIAC disease where the condition is one in which the heart fails to do its proper amount of work, UNLESS THE FAILURE IS DUE TO MYOCARDIAL DEGENERATION." *(From "Practical Therapeutics," A. J. Hare, 1916.)*

We have put in small capitals those parts of the original quotations which the Miles Medical Company either omits or modifies. It is worthy of note that the very next sentence in Hare's book, following the quotation just given, reads: "If simple hypertrophy or excessive compensatory hypertrophy exists, it [digitalis] is harmful." This statement the Miles concern does not quote, although it has in the past recommended the nostrum for cardiac hypertrophy.

Evidently the two ingredients meant are cactus and digitalis. It was considered that the presence or absence of these drugs could be best established by physiologic tests, and therefore a pharmacologist was asked to examine Dr. Miles' Heart Treatment. The question as to whether or not there is any cactus present was not considered of any special interest, because extensive experimental work has shown that cactus grandiflorus has no physiologic action. The tests that were made by the pharmacologist, however, were such that, had Miles' Heart Treatment contained any drug possessing any heart action, its presence would have been disclosed. The gist of the pharmacologist's report was to this effect:

> The tests indicated that there was no digitalis body present in the preparation (in amounts that could have any therapeutic effect) in doses containing enough alcohol to induce narcosis. There was no evidence that Miles' Heart Treatment has any therapeutic effect on the heart aside from that of the alcohol which it contains, even when administered orally, in doses corresponding to those of 1,750 c.c. for a man of 70 kilos. Such doses are equivalent to more than 7 bottles of the treatment. It can be said with certainty that Miles' Heart Treatment does not exert any action which entitles it to be considered as belonging to the digitalis group, or to any other group recognized by clinicians as exerting any typical, demonstrable, pharmacologic action on the heart.

In addition to the pharmacologic tests, Miles' Heart Treatment was also subjected to chemical analysis in the A. M. A. Chemical Laboratory. A summary of the chemist's report follows:

CHEMIST'S REPORT

"Chemical examination shows Miles' Heart Treatment to be a solution of a compound, or compounds, of iron representing about 0.120 gm. metallic iron in 100 c.c., or about ⅔ grain in one fluidounce. There is also a small amount of phosphate, about 5 per cent. of glycerin and a reducing substance, which may be glucose or invert sugar. No potent alkaloidal drugs could be detected. The presence of an ammonium compound was demonstrated by the liberation of free ammonia on addition of fixed alkali to the preparation. The liquid is colored with caramel. A solution of iron glycerophosphate in 10 per cent. alcohol with about 5 per cent. of glycerin and a little sugar or glucose had much the same chemical properties as Miles' Heart Treatment."

Concerning the nostrum THE JOURNAL commented as follows:

"How long would the 'patent medicine' business last if the exploiters of these nostrums were required to publish a full quantitative formula of the active ingredients on the label, and, further, were required to tell the truth about their products? The 'Latest and Greatest Discovery for Weak and Diseased Hearts,' which was 'the result of vast experience and years of Scientific Investigation by one of the most able and learned physicians of the age' does not loom as imposingly after it has been subjected to the test of independent chemical and physiologic investigation. A little iron, a small amount of phosphate, about 5 per cent. of glycerin, and 11 per cent. of alcohol, the mixture colored with caramel—a great discovery indeed!"

Details of Analysis

Dr. Miles' Heart Treatment was found to be a dark-colored liquid with a peculiar, ferruginous taste.

Specific gravity at 25 C.: 1.0271.

Total solids as determined by evaporation on a steam bath and subsequent drying to constant weight at 100 C. were 8.6188 gm. in 100 c.c.

Ash.—From 100 c.c. samples 0.2808 gm. and 0.276 gm., respectively, was obtained; average 0.2784 gm.

Caramel.—By the Amthor test (Leach, Food Inspection and Analysis, 1913, p. 752) caramel was detected.

Iron.—Iron was readily identified in the ash by dissolving the latter in dilute hydrochloric acid and adding ammonia water, potassium ferrocyanid, and potassium sulphocyanate to portions of the solution. Applying these tests directly to the Heart Treatment no reactions were obtained. Even boiling for some time with sodium hydroxid solution failed to precipitate ferric hydroxid. This peculiar behavior showed the iron to be present in the form commonly known as "masked."

The quantity of iron was determined by adding ammonium sulphid in excess to the Heart Treatment. After allowing it to stand several hours, the iron sulphid was collected and dissolved in hydrochloric acid and the iron in this solution was determined by precipitation as ferric hydroxid in the usual way after oxidation with nitric acid. The iron from 100 c.c. of the Heart Treatment amounted to 0.13104 gm. and a duplicate of 100 c.c. to 0.13048 gm.; average 0.13074 gm. of iron.

Phosphate.—The ash from the preparation contained phosphate as shown by the ammonium molybdate reaction. The Heart Treatment did not give the reaction direct, but after boiling a short time with nitric acid, it gave the molybdate reaction. This indicates phosphorus in the organic combination.

Glycerin.—This was determined by the method of the U. S. Department of Agriculture (Bureau of Chemistry, Bull. 107 Revised, p. 83) for wine. The glycerin from 100 c.c. of the Heart Treatment amounted to 4.3448 gm. and a duplicate gave 4.1580 gm., average 4.2514 gm.

Ammonia.—On heating the preparation with sodium hydroxid solution a faint odor of ammonia was noted. When distilled from excess of sodium hydroxid solution 100 c.c. of the Heart Treatment gave an alkaline distillate, requiring 4.004 c.c. of normal acid for neutralization; a duplicate required 3.636 c.c.; average 3.82 c.c. of normal acid. This indicates 0.0654 gm. of ammonia (NH_3).

Alkaloids.—A portion of the Heart Treatment was made alkaline with ammonia and extracted several times with chloroform. The residue left after evaporation of the chloroform gave no reaction for alkaloids by the usual alkaloidal reagents.

Sugar.—Portions of the Heart Treatment both before and after heating with acid reduced Fehling's solution. It was also slightly dextrorotatory. This may have been due to the caramel present.

LAVORIS

(Abstracted from The Journal A. M. A., Nov. 1, 1919, p. 1380)

Lavoris was considered by the Council on Pharmacy and Chemistry in 1913, and its proprietors—the Lavoris Chemical Company—were advised that the preparation was inadmissible to New and Nonofficial Remedies because of conflict with Rules 1, 4, 6, 8 and 10. No report was published at that time. As the preparation is still widely advertised to physicians, the Council has again examined Lavoris and authorized publication of the following report.

In recent years Lavoris has been widely advertised as "THE IDEAL ORAL ANTISEPTIC," particularly to the dental profession. A printed card sent out by the Lavoris Chemical Company in 1913 read: "LAVORIS, the Pyorrhea Remedy. The Original ZINC CHLORID Mouth Wash. One grain zinc to each ounce." The card also gave a "formula" to the effect that each pint of Lavoris contained:

Zinc Chlorid	1.040
Resorcin	0.520
Menthol	0.400
Saccharin	0.195
Formalin	0.195
Ol. Cassia Zeyl	0.780
Ol. Caryophyl	0.195

Advertisements now appearing in medical journals repeat the older "formula" except that resorcin is omitted. The formula, while seemingly frank and open, is in reality indefinite and misleading in that no denomination of weight is given for the various constituents. It is uncertain, for example, whether the figures in the formula are intended to represent grains, grams or percentages of the several constituents. In view of the indefinite statement of composition, a chemical examination of Lavoris was undertaken and the following report published in THE JOURNAL:

Zinc.—This was determined electrolytically. Fifty c.c. gave 0.026 gm. of zinc and 100 c.c. gave 0.0531 gm. of zinc. The average is 0.0526 gm. of zinc in 100 c.c. This is equivalent to 0.1102 gm. of anhydous zinc chlorid in 100 c.c.

Chlorid.—After decolorizing some Lavoris with chlorid-free animal charcoal, the chlorid was determined by the Volhard method. Twenty-five c.c. of Lavoris required 4.328 c.c. of tenth-normal silver nitrate solution, equivalent to 0.01535 gm. of chlorid (chlorid ion) or 0.0614 gm. in 100 c.c. A second 25 c.c. of Lavoris required 4.112 gm. of tenth-normal silver nitrate, equivalent to 0.01458 gm. of chlorid (chlorid ion) or 0.05832 gm. in 100 c.c. Average is 0.05985 gm. This is equivalent to 0.1150 gm. of zinc chlorid in 100 c.c. This agrees closely with the foregoing zinc determination.

Resorcin.—The method of the U. S. Pharmacopeia was used. The total bromin absorption of 25 c.c. of Lavoris was

3.68 c.c. of tenth-normal bromin. This is equivalent to 0.00675 gm. of resorcin in 25 c.c. or 0.02700 gm. in 100 c.c. In a duplicate test, 25 c.c. of Lavoris required 3.8 c.c. of tenth-normal bromin, equivalent to 0.00697 gm. of resorcin, or 0.02788 gm. in 100c.c. Since oil of cinnamon absorbs bromin, 50 c.c. of Lavoris was boiled until very little or no odor of the oil was noted, keeping the volume nearly constant by adding a little water from time to time, and the bromin absorption then taken. In one experiment, 0.36 c.c. of tenth-normal bromin was consumed, and in a duplicate no bromin was absorbed. This shows the absence of resorcin.

Residue.—On evaporating 25 c.c. of Lavoris on a steam bath and subsequent drying of the residue at 100 C., 0.0455 gm. of residue was obtained. This is equivalent to 0.1820 gm. in 100 c.c.

Saccharin.—Saccharin was detected in the residue and ether-extract of the residue by its intensely sweet taste after a little sodium bicarbonate had been added to it.

Formaldehyd.—This could be detected by the Jorissen test. The color was not very pronounced and the quantity of formaldehyd was small.

Oil of Cinnamon.—The odor and taste of Lavoris are characteristic of cinnamon.

Menthol and Oil of Cloves.—The odor of menthol and of oil of cloves could not be detected, but no tests were made to demonstrate their presence.

The analysis thus indicates that the Lavoris of today contains no resorcin but does contain a small amount of formaldehyd, a little saccharin, and oil of cinnamon (menthol and oil of cloves could not be detected by the odor, but were not tested for). The analysis showed that the principal constituent of Lavoris is zinc chlorid, of which there is about 0.1 gm. per 100 c.c. (about ½ grain to the ounce).

MICAJAH'S WAFERS AND MICAJAH'S SUPPOSITORIES

(Abstracted, with additions, from The Journal A. M. A. Nov. 29, 1919, p. 1715)

Micajah's Medicated Wafers (formerly called "Micajah's Medicated Uterine Wafers") were analyzed in the A. M. A. Chemical Laboratory in 1910.* They were found to consist essentially of dried ("burnt") alum, boric acid and borax, in approximately the following proportions:

---

* Comparative analyses of Micajah's Wafers and Piso's Tablets were made in the Association's Laboratory in 1915. (Annual Reports Chem. Lab. A. M. A. **8**: 100.)

	Per Cent.
Alum, dried	59.86
Borax, dried	15.62
Boric acid	5.67
Water of hydration	18.85

There are a number of drugs that are more or less effective in the treatment of local lesions of mucous membranes and the skin. They are classed as astringents Among these are included alum, borax and boric acid. Every physician has used them. To say that a wafer consists of alum, borax and boric acid inspires but little awe. But there is something much more mysterious and impressive in declaring that a wafer "consists of an astringent and antiseptic base, in which are incorporated certain medicaments which both locally and after absorption, contribute to the astringent, antiphlogistic, depletive, soothing and healing action of the product." This gives the impression that some powerful and almost incomprehensible factors are at work. Yet, after all is said and done, the substances contained in Micajah's Medicated Wafers are just the homely old alum, boric acid and borax.

In addition to "Micajah's Medicated Wafers," Micajah and Co. also put out "Micajah's Suppositories for Hemorrhoids." These have been examined in the A. M. A. Chemical Laboratory and, like the "Medicated Wafers," have been found to contain alum, boric acid and borax—and these substances practically alone—incorporated in cacao butter. The company claims that "to these have been added Ammonii Ichthyosulphonate, Balsam of Peru, Ext. Belladonae." The A. M. A. chemists report, however, that if extract of belladonna is present at all it is in amounts too small to be detected by the method commonly employed in the chemical examination of alkaloidal drugs. The chemists report further that while ammonium ichthyosulphonate and balsam of Peru both have a decided odor and are dark in color, the suppositories have but little color and the odor of the cacao butter that forms their base is not covered by these drugs; obviously, therefore, if ammonium ichthyosulphonate and balsam of Peru are present at all they are in amounts utterly insufficient to exert any therapeutic effect.

Details of Analysis

Micajah's Suppositories have a slight greenish color and the characteristic odor of cacao butter.

One suppository weighed 1.812 gm., or about 28 grains.

A suppository was extracted with chloroform. The residue of fat, after drying on a steam bath for three hours, weighed 1.4416 gm. The fat was of a pale straw color. Therefore very little if any balsam of Peru could be present. The residue insoluble in choloform was colorless and therefore very little if any ammonium ichthyosulphonate could be present. No odor of either of these drugs could be detected in the suppositories.

On ignition a residue remained that responded to the usual tests for sulphate and for aluminum. Alcohol was added to a portion of this residue and the solvent ignited. The alcohol burned with the green mantle peculiar to boric acid.

Alkaloids.—Two suppositories were extracted several times with chloroform and alcohol, about equal volumes. This solution was then shaken out with acid, the acid extract made alkaline and extracted with several small portions of chloroform. The chloroform was allowed to evaporate and the residue taken up with very dilute acid. The acid solution gave no alkaloidal reactions with iodin test solution nor with potassium mercuric iodid test solution This was taken to indicate the absence of belladonna extractives, at least in quantities more than mere traces.

CHLORON, CHLORAX AND NUMBER "3"

(Abstracted, with additions, from the Annual Reports of the Council on Pharmacy and Chemistry, 1919, p. 70)

Chloron, Chorax and Number "3" are preparations of essentially similar composition put out by the Chlorine Products Company, Inc., New York.

Chloron.—Chloron, according to the label, is "A stable CHLORINE remedy for the reduction of inflammation, relief of pain and for all wounds, burns, scalds and every description of sores except cancer and lupus." Its composition is given as:

> "Free chlorine, 0.200 per cent.; Calcium chloride, 0.190 per cent.; mercurous chloride, 0.030 per cent.; lithium chloride, 0.035 per cent.; calcium hydrate, 0.010 per cent.; water to 100 parts."

The Council asked the manufacturers for further information in regard to the composition or preparation of Chloron and received this reply:

> "Chlorine gas is prepared in the usual way and purified and passed into water until a saturated solution is made.
>
> "Water to the extent of three times the volume of the chlorine solution is used to dissolve the necessary amount of calcium chloride, and the two solutions are mixed.
>
> "The necessary amounts of Lithium and Mercurous Chloride are then intimately mixed and made into solution. This solution is then added to the above and the whole is agitated for some minutes."

A specimen of Chloron was examined in the A. M. A. Chemical laboratory and the chemists reported:

Qualitatively the presence of the following constituents was confirmed: calcium, mercury, lithium, chlorid, free chlorin. The solution was alkaline. Of course, the declaration that Chloron contains mercurous chlorid (calomel) is obviously incorrect, as mercurous chlorid cannot exist in a solution containing active chlorin (Cl^+) but is oxidized to mercuric chlorid (corrosive sublimate). As the solution was alkaline in reaction, it seemed unlikely that all the active chlorine was present in the free state, as declared on the label. The quantitative estimation of "free chlorine" was determined according to the method described in *New and Nonofficial Remedies*, 1918, p. 153. The active (so-called available) chlorin was determined by the usual method of the U. S. Pharmacopeia for solution of chlorinated soda. In the specimen of Chloron examined (which had been kept in the dark) the amount of free chlorin was 0.036 per cent. and the total amount of "available" chlorin was 0.330 per cent., or 165 per cent. of the claimed amount.

A comparison of the information sent to the Council with the analytic findings leads to the conclusion that Chloron is not of reliable composition.

Attention should be called to the fact that the amount of active chlorin, claimed to be present in Chloron as well as the amount found by the association laboratory, is less than that considered effective by Dakin, Dunham and others; seemingly in preparing Chloron no attention has been paid to the degree of alkalinity, yet the importance of this factor is now generally recognized.

Chloron fails to comply with the requirements for surgical solution of chlorinated soda (N. N. R., 1919, p. 133), yet the manufacturers make free use of the text of Dakin and Dunham's Handbook of Antiseptics in their advertising pamphlet. Thus:

From the Chloron pamphlet:	Dakin and Dunham Handbook of Antiseptics:
"This ideal antiseptic effects complete sterilization within its sphere of action without causing any damage to the cells or tissues. An important method of judging the injurious action of antiseptics is to investigate their effects on the leucocytes. From experiments *in vitro* by Parry Morgan and *in vivo* by Col. C. J. Bond with the strength of antiseptics commonly used in surgery, it has been found that Chlorine antiseptics and mercury salts have little effect on phagycytosis in comparison with other germicides. The activity of the leucocytes from wounds which have recently been treated with CHLORON may be demonstrated experimentally."	"The ideal surgical antiseptic should effect complete sterilization within its sphere of action without causing any damage to animal cells. At the moment such a substance does not appear likely to be found, but on the other hand it is surprising to see how little damage may be done to animal tissues by some active antiseptics. An important method of judging of the injurious action of antiseptics is to investigate the condition of the leucocytes in wounds recently treated with the substance under consideration. In general it appears from experiments *in vitro* that, with the strength of antiseptics commonly used in surgery, mercury salts and hypochlorites have relatively little effect on phagocytosis as compared with phenol (Parry Morgan). It is a regular phenomenon to observe activity of the leucocytes obtained from wounds which have been recently treated with hypochlorites. Ingenious methods for determining the influence *in vivo* of antiseptics on the activities of leucocytes have been worked out by Col. C. J. Bond."
"In addition to its antiseptic action CHLORON is a strong oxidizing agent and deodorant and possesses to a marked degree the property of decomposing toxins. In this connection it is interesting and pertinent to note that Dean, by the regulated action of hypochlorous acid, has prepared a nontoxic dysentery vaccine and it is now a common observation that the free use of CHLORON may reduce the constitutional symptoms arising from septic processes and that they reappear on discontinuing the antiseptic treatment."	"In addition to their disinfecting action, the Chlorine antiseptics are strong oxidizing agents and deodorants and moreover possess in high degree the property of decomposing toxins. By the regulated action of hypochlorous acid, Dean has prepared a nontoxic dysentery vaccine and it is a common observation that the free use of hypochlorites may reduce the constitutional symptoms arising from septic processes and that they reappear on discontinuing the antiseptic treatment."

Chlorax.—Chlorax is said to be "A stable CHLORINE solution for internal use," in "Kidney Conditions," "Diabetes," "Acute Infections," "Blood Dyscrasias," "Lithemias and Rheumatism," and "Nervous Conditions." It is claimed to have the same composition as that of Chloron with the addition of 0.016 per cent. of tincture of opium.

The A. M. A. Chemical Laboratory reported that the free chlorin in Chlorax was 0.01 gm. per hundred c.c. and the total amount of active ("available") chlorin was 0.25 gm. per hundred c.c., or 125 per cent. of the amount claimed. The laboratory notes that though the chlorin content of Chloron and Chlorax is claimed to be the same, that of Chlorax actually is less. This is not surprising when the presence in Chloron of reducing substances such as alcohol is borne in mind. The laboratory concludes that Chlorax is not of reliable composition.

Number "3"

According to the label, Number "3" is "A STABLE CHLORINE remedy for the purification of the blood," with the composition:

"Free Chlorine, 0.35 per cent.; Calcium Chloride, 0.30 per cent.; Mercurous Chloride, 0.03 per cent.; Lithium Chloride, 0.04 per cent.; Calcium Hydrate, 0.01 per cent.; Opium, 0.02 per cent.; Ethyl Alcohol, 0.10 per cent.; water to 100 parts.

It will be noticed that the composition claimed for Number "3" is essentially similar to that claimed for Chloron. It differs from Chloron in that the amounts of some of the constituents are somewhat greater, and in that, like Chlorax, it contains some tincture of opium.

The A. M. A. Chemical Laboratory reports that the free chlorin in a specimen of Number "3" was 0.024 gm. in 100 c.c. and the total active ("available") chlorin 0.173 gm. per hundred c.c., or about 50 per cent. of the claimed amount. The examination indicates that Number "3" is of unreliable composition. The Chlorine Products Company, Inc., submitted no clinical evidence for Number "3" to which it refers as "our Syphilis remedy." It stated that two physicians had used the preparation "with good results," and admitted that "the company requires further evidence before pushing it."

In commenting on the products, The Council declared "Chloron," "Chlorax" and "Number 3" in conflict with the rules governing admission to New and Nonofficial Remedies. All are of unreliable composition (conflict with Rule 1). The therapeutic claims made for the preparations are not substantiated by acceptable evidence and are unwarranted and misleading. Chloron is inferior as an antiseptic to the well-known surgical solution of chlorinated soda on account of its low chlorin content and uncontrolled reaction. There is no warrant for the claim that Chlorax is useful in the treatment of "Kidney Conditions," "Diabetes," "Acute Infections," "Blood Dyscrasias," "Lithemias and Rheumatism," and "Nervous Conditions," nor is there warrant for the claim that "Number 3" is a remedy for the purification of the blood or a "Syphilis remedy" (conflict with Rule 6).

The names of these pharmaceutical mixtures are not descriptive of their composition (conflict with Rule 6).

All three preparations are irrational. No evidence has been furnished that the lithium salt is of value in the mixtures. It is not rational to combine an active chlorin preparation and a mercury salt in one mixture, nor is there evidence that the addition of opium to the preparations proposed for internal use is of value or rational. Experimentation with Number "3" as a "Syphilis remedy" is to be severely condemned in that those on whom it is used will in the meantime be deprived of efficient medication (conflict with Rule 10).

Department
of
Pharmacology
University
of
Toronto

PART III

REPORTS NOT PREVIOUSLY PUBLISHED

NOTE ON MELTING POINT OF ACETYLSALICYLIC ACID

Paul Nicholas Leech, Ph. D.

As stated in a previous communication,[1] the melting point of acetylsalicylic acid has been given at various temperatures (from 118 to 139 C.). This variation may be attributed to two reasons: a difference in the relative purity of the product, or, the manner in which the melting point is taken. As it has been found that practically any standard brand of acetylsalicylic acid *now* made in this country is of a high degree of purity, the discrepancies which still arise in reporting melting points must be due to the method employed in their determination.

In the article referred to above, it was suggested that the method of taking the melting point should be that of the ninth edition of the U. S. Pharmacopeia modified by first heating the bath to 120 C. before attaching the melting point tube to the thermometer. By this procedure the melting point of pure acetylsalicylic acid was found to be 131.5-132.5 C. (cor.). As a liberal range, 128-133 C. was suggested as a standard, inclusive of the better products on the American market in 1917.

Dahm has described recently a rather elaborate apparatus for determining the melting point of acetylsalicylic acid;[2] but the chief difference in his method from that described by the writer is that the melting point tube is not immersed until the bath has obtained a temperature of 130 C. Dahm believes that the range of melting point should be from 133 to 135 C. when taken by his method. He found that various brands of acetylsalicylic acid had higher melting points than those reported previously by the writer though comparative results were the same. The average melting point of the specimens examined by Dahm according to his method averaged about 133.5 to 134.5 C.

---

1. Leech, P. N.: Examination of American-Made Acetylsalicylic Acid, Jour. Ind. Eng. Chem. **10**: 4, 228 (April) 1918.
2. Dahm, H. L.: Some Notes on Acetylsalicylic Acid, Ibid., January, 1919, p. 29.

Andrews and Herron[3] analyzed different brands of acetylsalicylic acid. They report that those specimens assaying 99.0 per cent. acetylsalicylic acid had a melting point of from 133 to 135 C., while the samples assaying 99.9 per cent. gave a melting point of 139 C. The writer communicated with Drs. Andrews and Herron, who kindly sent two samples of acetylsalicylic acid of high melting point. These two specimens, as well as a specimen of acetylsalicylic acid-Monsanto, were examined for free salicylic acid and particularly as to the melting point; the latter offered the opportunity to compare the methods of Dahm and of the writer.

One gram of each specimen was dried in a watch glass over sulphuric acid for twenty-four hours. Free salicylic acid (by method described in previous paper) was absent in two samples (A and M) and there was less than 0.1 per cent. in the third sample (B). The three samples all melted at 132.0-132.5 by the method of the writer (immersing the tube in the bath at 120 C.).

The same apparatus being used but the melting point tubes being immersed when the temperature of the bath was 130 C. (suggested by Dahm), the three specimens were found to melt at 134.5-135 C. The difference in the two melting points is in accord with the reported observations that the melting point of acetylsalicylic acid may be depressed 1 degree or more for every five minutes of heating.

The method of Dahm has the advantage that the acetylsalicylic acid is subjected to less decomposition by heat (equivalent to about 2 degrees degression in melting point) than when placed in the bath at 120 C. Dahm's method, on the other hand, has the disadvantage in that some inferior product could apparently melt at about 130 C., when, according to work done in the A. M. A. Chemical Laboratory, there have been specimens on the market which melted as low as 128 C. (immersed at 120 C.).

The observations of Andrews and Herron may be due to rapid heating; the Pharmacopeia prescribes 0.5 degree rise in temperature per minute when substance is near melting.

The writer is inclined to prefer heating the bath to 120 C. rather than to 130 C., before immersing the melting point tubes. He fells, however, there is now no longer any necessity for a range as low as 128, and recommends that the standard range should be from 130 to 133 C.

---

[3] Andrews, L. T. and Herron, C. S.: A Simple Method for Acetylsalicylic Acid Assay, Am. & Pharm. Rev., March, 1919, p. 25.

THE EXAMINATION OF ACRIFLAVINE AND PROFLAVINE

L. E. Warren, Ph.C., B.S.

It has been known for some time that certain dyes possess bactericidal and amebicidal properties, while others have no effect as antiseptics or germicides. After this discovery was made, chemical research was begun in the effort to produce substances that should have higher bactericidal potencies than those already known. In these studies it was found that certain of the acridin derivatives were especially active as amebicides. Acridin is a substance first obtained from coal tar. Some of its derivatives have been known and used as dyes for many years,[1] certain of them being known as "flavines"[2] because of the yellow color that they impart to fabrics. Previous to the opening of the World War the manufacture of the acridin dyes was entirely controlled by the Germans through an extended patent monopoly.[3]

Most of the acridin derivatives have no amebicidal properties; but, as already stated, there are some marked exceptions. One of these (diamino methyl acrdin chlorid) was found by Ehrlich to have notable therapeutic effects in trypanosome infections and, on this account, he called it "Trypaflavine." This is now known as "acriflavine." A closely related substance having similar properties is "proflavine." Proflavine is 3:6 diamino acridine sulphate, $C_{13}H_{11}N_3H_2SO_4H_2O$. Acriflavine is 3:6 diamino-10 methyl acridine chlorid, $C_{14}H_{14}N_3ClH_2O$. These substances were first prepared by Benda.[4] Most of the studies on these substances, both bacteriologic and clinical, have been conducted by English investigators.[5]

After the World War opened the need of antiseptics in wound treatment led the British Medical Research Committee[6] to study the various antiseptics in a comparative way. Drs. Barger and Ewins prepared acriflavine, and the substance was tested by Browning and his assistants in the Middlesex Hospital. The substances compared included chlorin water, several forms of the hypochlorites, phenol, mercuric chlorid, iodin dissolved in an aqueous solution of potassium iodid, brilliant green (oxalate and sulphate), malachite green (oxalate and sulphate), crystal violet, ethylhydrocuprein and acriflavine. The bacteriologic studies were supplemented by more than 2,000 clinical trials. Acriflavine is claimed by Browning and his associates to have high antiseptic power, together with freedom from toxic or irritant action, and without inhibiting effects on the phagocytic action of the leukocytes or on the healing processes. Acriflavine and proflavine have been extensively used in the treatment of wounds, and acriflavine has been highly praised in the treatment of gonorrhea. Proflavine oleate in the form of an ointment has also been used.

In view of the interest manifested in the therapeutic properties of acriflavine and related compounds, as evidenced by numerous inquiries to the Council on Pharmacy and Chemistry of the American Medical Association from physicians and others, it seemed worth while to make a chemical examination of the market supplies of the products. This appeared desirable owing to the lack of adequate published information concerning the tests for identity and purity of the substances that were being used in medicine. Accordingly specimens of the avilable brands of acriflavine and proflavine were obtained. One specimen of proflavine base was available and this was included in the examination. Proflavine base has not been much used in this country, but in Europe it has found some application in the form of ointments, probably because of its more ready solubility in oils and fats.

The reported favorable results from the experimental use of acriflavine in wound treatment led British manufacturers to produce the drugs on a commercial scale, and at least one English brand is being imported into the United States. Two brands were obtained from American manufacturers. A specimen each of acriflavine, proflavine and proflavine base was obtained from the Heyl Laboratories, Inc., of Chicago, through The Sargent's Drug Stores as agents; a specimen each of acriflavine and proflavine from The Boots Pure Drug Co., Ltd., through the American agents, Hynson, Westcott and Dunning, and a specimen each of acriflavine and proflavine from the Research Laboratories of Chicago.

Being recently introduced drugs, naturally there is but little published information concerning tests for identity and purity of acriflavine and proflavine. Benda[4] briefly described the properties of each substance and gave some tests to differentiate between the two. However, his descriptions are not sufficiently detailed to be of much use in determining the quality of commercial products. Some information in these directions was also furnished by the manufacturers or their agents through correspondence. Therefore, it became necessary to compile and devise tests by which the identity and purity of the commercial specimens might be judged. Accordingly provisional tests were devised that were based on the published information, and, as the work progressed, these were modified and amplified as found necessary by the results obtained in the examination.

Solubilities.—No information concerning the solubilities of acriflavine and proflavine was found in the literature except that they were soluble in water and alcohol. Since the substances are used in therapy only in great dilution (1 : 1,000-1 : 8,000) accurate solubility values are not of great consequence to pharmacists or physicians. As a matter of interest, however, the solubility of the two substances was approximately determined at the temperature of the laboratory (about 24 C.). Acriflavine is soluble in less than 2 parts of water, and proflavine is soluble in about 220 parts of water. The solubility of each is less in alcohol but sufficient for any purpose likely to be required in therapy. Each substance is soluble in methyl alcohol and somewhat soluble in glycerol.[7] Neither substance is soluble, except to a slight degree, in other solvents in ordinary laboratory use, such as ether, chloroform, amylic alcohol, acetone, carbon bisulphid, carbon tetrachlorid, petroleum benzin, benzene, liquid petrolatum, and fixed and volatile oils.

Other than solubilities the determinations were limited to loss on drying, ash and insoluble matter. In proflavine, in addition, an attempt was made to determine the sulphate content by precipitation with barium chlorid and weighing as barium sulphate, but the results were not satisfactory. The analytical findings are given in Tables 1 and 2.

Loss on Drying.—A weighed quantity of the material was dried at 100 C. to constant weight.

Ash.—A weighed quantity of the material was ignited in a porcelain crucible. In some cases difficulty was encountered in burning the last portions of carbon. The trouble was overcome by moistening the cooled ash with ammonium nitrate solution, drying and again heating. If necessary the treatment with ammonium nitrate was repeated until constant weight was attained.

Insoluble Matter.—A weighed quantity of the material was dissolved so far as possible in a large excess of warm water, the insoluble matter collected in a weighed Gooch crucible, washed alternately with water and alcohol until the washings were practically free from fluorescence, and the residue dried at 100 C. and weighed.

Sulphate in Proflavine.—A weighed quantity of proflavine was dissolved in a considerable excess of warm water, the solution filtered, the filtrate slightly acidulated with hydrochloric acid, an excess of barium cholrid solution added, the mixture allowed to stand over night, the precipitate collected in a weighed Gooch crucible, heated and weighed in the usual way. The results were calculated to proflavine containing one molecule of water of hydration. The findings were exceedingly variable. Nevertheless they are given as a matter of record.

TABLE 1

Brand	Loss on Drying, per cent.	Water Insoluble, per cent.	Ash, per cent.
Acriflavine Heyl............................	4.33	1.29	0.61
Acriflavine Boots...........................	7.27	....	0.10
Acriflavine Research.......................	7.73	....	0.24
Theory......................................	6.49	....	....

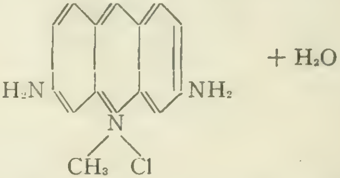
TABLE 2

Brand	Loss on Drying	Water Insoluble	Ash	By $BaSO_4$ (Hydrated Form)
Proflavine Heyl...............	7.52	2.81	0.38	110.88 109.92 109.59
Proflavine Boots..............	4.38	0.10	0.26	101.13 104.56
Proflavine Research...........	3.41	....	Unweighable	99.28 100.32
Theory........................	5.54	....	....	......
Proflavine base Heyl..........	12.88	5.20	3.29	......

From the results of the analysis it may be seen that the products of the Heyl Laboratories, Inc., are inferior to those of the other brands examined. The others conform to the tentative tests suggested.

Based on the information compiled from the literature of the acridine dyes, supplemented by deductions from the results obtained in the study of the several commercial specimens of acriflavine and proflavine, tentative monographs for the several substances examined were prepared. It should be understood that the descriptions given do not attempt to include all of the tests known but only such as appeared to be adequate to establish the identity of the substances in question and to insure products of a sufficient degree of purity for medicinal purposes. Although the tests and standards are tentative in nature, it was considered worth while to publish them in the belief that they might prove useful to analysts and to manufacturers. Criticisms of the tentative monographs are invited.

ACRIFLAVINE.—3:6 diamino-10 methylacridine chloride = $C_{14}H_{14}N_3Cl.H_2O$.



Acriflavine is a brownish-red, odorless, crystalline powder. It is soluble in less than 2 parts of water and in alcohol, forming dark red solutions which fluoresce on dilution and which have a bitter taste. Nearly insoluble in ether, chloroform, liquid petrolatum, fixed oils and volatile oils.

An aqueous solution of acriflavine (1: 250) is neutral to litmus paper (it dyes the litmus paper yellow).

Add a few drops of hydrochloric acid to an aqueous solution of acriflavine, which is sufficiently dilute to be fluorescent. The fluorescence disappears, but partially reappears on further dilution with water.

Add 2 drops of sulphuric acid to about 1 c.c. of an aqueous solution of acriflavine (1: 250) and agitate the mixture. An orange-red, crystalline precipitate is produced. Under the microscope the crystals are seen to be mostly long needles or prisms arranged in sheathlike or brushlike forms.

An aqueous solution of acriflavine (1: 250) gives a precipitate with silver nitrate solution (*distinction from proflavine*).

An aqueous solution of acriflavine (1: 250) does not give a precipitate with barium chlorid solution (*distinction from proflavine*).

An aqueous solution of acriflavine (1: 250) does not give a precipitate with formaldehyde solution (*distinction from proflavine, which gives a brown precipitate*).

Add 2 drops of diluted hydrochloric acid to 5 c.c. of an aqueous solution of acriflavine (1: 250) and immediately add 2 drops of sodium nitrite solution (1: 10). A violet color is produced. By the further addition of an excess of sodium nitrite solution, a violet precipitate is formed and, after a few minutes, the color of the solution becomse cherry-red. This may be best observed after filtration (*distinction from proflavine, the filtrate from which is colorless*).

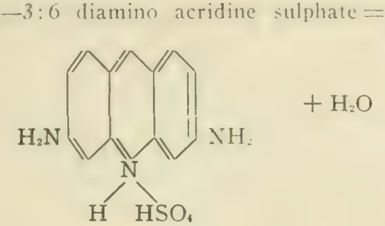
An aqueous solution of acriflavine (1: 250) gives an orange precipitate with sodium hydroxid test solution (*distinction from proflavine, which gives a yellow precipitate*).

Incinerate about 1 gm. of acriflavine, accurately weighed. The ash amounts to not more than 1 per cent.

Dissolve about 1 gm. of acriflavine, accurately weighed, in 250 c.c. of warm water, collect the insoluble matter, if any, in a weighed Gooch crucible, wash the insoluble matter with hot water, dry and weigh the residue. The insoluble matter amounts to not more than 1 per cent.

Dry about 1 gm. of acriflavine, accurately weighed, to constant weight at 100 C. The substance loses not more than 10 per cent. of its weight.

PROFLAVINE.—3 : 6 diamino acridine sulphate = $C_{13}H_{11}N_3H_2SO_4H_2O$.



Proflavine is a reddish-brown, odorless, crystalline powder.

Proflavine is soluble in water and in alcohol, forming brownish solutions which fluoresce on dilution. Nearly insoluble in ether, chloroform, liquid petrolatum, fixed oils and volatile oils.

An aqueous solution of proflavine is neutral to litmus paper (the solution dyes the litmus paper yellow).

Add a few drops of hydrochloric acid to an aqueous solution of proflavine, which is sufficiently dilute to be fluorescent. The fluorescence disappears, but partially reappears on dilution with water.

Add 2 drops of sulphuric acid to about 1 c.c. of an aqueous solution of proflavine (1: 250), and agitate the mixture. A brown, crystalline precipitate is produced. Under the microscope the crystals are seen to be mostly prismatic needles.

An aqueous solution of proflavine (1: 250) gives a precipitate with barium chlorid solution (*distinction from acriflavine*).

An aqueous solution of proflavine (1:250) gives no precipitate with silver nitrate solution (*distinction from acriflavine*).

Add a few drops of formaldehyde solution to 5 c.c. of an aqueous solution of proflavine (1:250). A brown precipitate is given (*distinction from acriflavine which remains clear*).

Add 2 drops of diluted hydrochloric acid to 5 c.c. of an aqueous solution of proflavine (1: 250) and, immediately add 2 drops of sodium nitrite solution (1: 10). A violet color is produced. On the further addition of sodium nitrite solution a brownish violet precipitate is formed and, after a few minutes, the solution becomes colorless. This may be best observed after filtration (*distinction from acriflavine, the filtrate from which becomes cherry-red*).

An aqueous solution of proflavine (1: 250) gives a lemon yellow precipitate with sodium hydroxid solution (*distinction from acriflavine, which gives an orange precipitate*).

Incinerate about 1 gm. of proflavine, accurately weighed. The ash amounts to not more than 1 per cent.

Dissolve about 1 gm. of proflavine, accurately weighed, in 250 c.c. of warm water, collect the insoluble matter, if any, in a weighed Gooch crucible, wash the insoluble matter with hot water, dry and weigh the residue. The insoluble matter amounts to not more than 1 per cent.

Dry about 1 gm. of proflavine, accurately weighed, to constant weight at 100 C. The substance loses not more than 10 per cent. of its weight.

---

1. Ber. d. deutsch. chem. Gesellch. **15**: 2173, 1882; **27**: 2320, 1894; **32**: 2363, 1899; **33**: 905, 912 and 2470, 1900; **34**: 4307 and 4317, 1901; **36**: 590, 1903; **38**: 3787, 1905, and **45**: 1787, 1912.

2. The use of the word *flavine* as applied to the acridine dyes is being discouraged because of confusion with the name *flavine* which is sometimes applied to the vegetable coloring substance *quercetin*.

3. D. R. P. 59,179; 75,755; 79,250; 79,703; 120,466; 121,686; 131,365; 132,116; 230,412 and 243,085. British patent 24,652, 1910; U. S. patents 739,117 and 759,187.

4. Benda, L.: Ueber das 3: 6—Diamino-Acridin, Ber. d. deutsch. chem. Gesellsch. **45**: 1787, 1912.

5. A large number of papers, chiefly of clinical interest, have appeared. For an extended bibliography of the subject see the Reports of the Council on Pharmacy and Chemistry of the A. M. A., 1919, p. 38.

6. Browning, C. H.; Gulbransen, R.; Kennaway, E. L., and Thornton, L. H. D.: Flavine and Brilliant Green, Powerful Antiseptics with Low Toxicity to the Tissues: Their Use in the Treatment of Infected Wounds, Brit. M. J. **1**: 73, 1917.

7. A solution of acriflavine in glycerol may be prepared conveniently by dissolving 1 part of the dye in 3 parts of water and mixing the solution with the requisite quantity of glycerol.

THE EXAMINATION OF COMMERCIAL BARBITAL-SODIUM

L. E. Warren, Ph.C., B.S.

Barbital is a name selected by the Federal Trade Commission for the substance, diethylbarbituric acid (diethyl malonyl urea). Barbital was introduced into medicine under the protected name "veronal." In England it is known as "barbitone." Barbital-sodium is the sodium salt of diethylbarbituric acid. It was introduced under the protected names "veronal-sodium" and "medinal."

Two specimens of barbital-sodium Abbott were received from the manufacturer, The Abbott Laboratories, one (Specimen A), May 14, 1919, and the other (Specimen B), June 4, 1919. Two specimens of medinal were examined, one of which was received from the manufacturers, Schering and Glatz, of New York, and the other was purchased on the open market. Two specimens of veronal-sodium were received from the manufacturer, Winthrop Chemical Co. of New York. A specimen of tablets of veronal-sodium and a specimen of tablets of medinal were received, each having been sent by its respective manufacturer. Each specimen was submitted to examination.

Several specimens of barbital-sodium were examined during 1918, and a report on that examination was published in the Annual Reports of the Chemical Laboratory of the American Medical Association, 1918, p. 56. The analytical methods there detailed were followed in this examination, except that in the barbital determination the separated barbital was dried over sulphuric acid to prevent loss by volatilization. The analysis was limited to tests for foreign metals, tests for uncombined diethylbarbituric acid, determinations of loss on drying, sodium content and the barbital yield on treatment with an acid and extraction with ether. In the ether extraction it was found necessary to make from six to eight shakeouts before extraction of barbital was complete.

Abbott Brand Specimen.—Specimen A lost 0.41 per cent. of its weight on drying, contained 10.82 per cent. of sodium and yielded 87.31 per cent. of barbituric acid. Specimen B lost 0.44 per cent. of its weight on drying, contained 10.67 per cent. of sodium and yielded 87.57 per cent. of barbital. The barbital from each specimen melted sharply at 188-9 C. Foreign metals and uncombined barbital were absent. According to theory, barbital-sodium should contain 11.16 per cent. of sodium and should yield 89.33 per cent. of barbital on treatment with an acid. The results indicate that, although each specimen is slightly below theory in respect to its sodium content and its yield of barbital, the composition is essentially as claimed.

Medinal.—The specimen of medinal received from Schering and Glatz, Inc., was so small that duplicate determinations were not made. The specimen lost 0.16 per cent. of its weight on drying, contained 11.04 per cent. of sodium, determined as sodium sulphate (without making allowance for the presence of traces of lead) and yielded 88.8 per cent. of barbital. The separated barbital melted at 188 C. Since, according to the formula, theory requires 11.16 per cent. of sodium and a yield of 89.33 per cent. of barbital, the preparation has essentially the composition claimed for it. Traces of lead were present, but the amount was insufficient to respond to the test for heavy metals according to the test as outlined in the U. S. P. IX under sodium salicylate.

Because of the presence of lead in the submitted specimen of medinal a market specimen of the product was purchased and the lead in the specimen determined. The amount found was equivalent to 0.01 per cent. of basic lead carbonate $(PbCO_3)_2Pb(OH)_2$, although the form in which the lead exists in medinal was not positively determined. Although lead occurs only in very small amounts in the specimen, there would appear to be no reasonable excuse for its presence, since there are other brands of barbital-sodium on the market which contain none. The specimen lost 0.33 per cent. of its weight on drying at 120 C., contained 10.95 per cent. of sodium, determined as sodium sulphate (without making correction for the presence of traces of lead) and yielded 88.57 per cent. of barbital. The separated barbital melted at 188 C. Uncombined barbituric acid was absent. It may be seen from the analysis that the product has substantially the composition claimed.

Veronal-Sodium Winthrop and Tablets of Veronal-Sodium Winthrop.—A specimen of veronal-sodium was submitted by the Winthrop Chemical Co. The package bore a typewritten label. No claims concerning the quality of the product were made on the label. The substance was a pale cream-colored powder, having a faint empyreumatic odor. It was soluble in water (with the exception of a small quantity of a granular, white powder), the resultant solution being of a pale-yellowish, not very desirable, color. The insoluble residue responded to tests for lead and effervesced with acids from which it was concluded to be lead carbonate. The lead in the preparation was determined and the quantity found was equivalent to 0.49 per cent. of basic lead carbonate $(PbCO_3)_2 Pb(OH)_2$. Before the presence of lead had been demonstrated sodium had been determined as sodium sulphate. Allowance was afterward made in the calculations for the presence of lead sulphate in the residue of sodium sulphate as weighed. The sodium sulphate obtained (after correction) corresponded to 11.21 per cent. of sodium (theory requires 11.16 per cent.

Veronal (barbital) was determined, the amount found being 88.44 per cent. (theory 89.33 per cent.). The separated barbital melted at 187-8 C. Uncombined barbital was absent. Moisture was determined by drying at 120 C. The loss amounted to 0.29 per cent.

Evidently the specimen of veronal-sodium examined is a rather crude grade of the product. The presence of nearly 0.5 per cent. of a toxic substance (lead carbonate or painter's "white lead") is very undesirable. The maximum dose of veronal-sodium (N. N. R. 1918) is given as 15 grains. The patient taking this quantity would receive $^{7}/_{100}$ grain of lead carbonate. There can be no valid excuse for the presence of lead in veronal-sodium since another brand of the product (barbital-sodium Abbott) is free from this impurity.

Tablets Veronal-Sodium Winthrop.—The tablets are claimed to contain 5 grains of veronal-sodium each. Qualitative tests for lead were made and traces of the metal were detected. Quantitative tests for lead were not carried out.

The Winthrop Co. was notified of the presence of lead in its specimen of veronal-sodium. The firm then submitted another specimen. This was found to be free from lead but was found to contain nearly 1 per cent. of uncombined barbital. This specimen lost 0.73 per cent. of its weight on drying, contained 10.92 per cent. of sodium and yielded 88.78 per cent.

of barbital (including the uncombined barbital). The firm stated that the products containing lead as an impurity were not put on the market.

The findings for the several specimens are given in the accompanying table:

ANALYSIS OF BARBITAL-SODIUM

Brand	Loss on Drying, per Cent.	Sodium, per Cent.	Yield of Barbital, per Cent.	Melting Point of Barbital	Lead as Basic Lead Carbonate	Uncombined Barbital
Barbital-sodium A—Abbott	0.41	10.82	87.31	188-9C.	Absent	Practically none
Barbital-sodium B—Abbott	0.44 (0.78 at 150°)	10.67	87.57	188-9C.	Absent	Practically none
Medinal (submitted)	0.16	11.04 (uncorrected for lead)	88.80	188C.	Present	
Medinal (purchased)	0.33	10.95 (uncorrected for lead)	88.63	……..	0.01 per Cent.	
Vernoal-sodium A—Winthrop	0.67	11.21 (corrected for lead)	88.44	187-8C.	0.49 per Cent.	
Veronal-sodium B—Winthrop	0.67 (at 150°) 0.13 (over H_2SO_4)	10.92	88.78	……..	Absent	0.96 per Cent.
Theory…………	….	11.16	89.33	188C.		

Details of Analysis

BARBITAL-SODIUM ABBOTT

Loss on Drying.—Weighed quantities of the material were dried at 120 C. until no further loss in weight occurred.

Specimen A.—From 1.1279 gm., a loss of 0.0045 gm. was noted, or 0.399 per cent.; from 1.2373 gm., a loss of 0.0051 gm. was observed, or 0.412 per cent.; average 0.405 per cent. loss.

Specimen B.—From 1.0049 gm. of material a loss of 0.0055 gm. was obtained or 0.457 per cent.; a duplicate of 1.0119 gm. gave 0.0049 gm. loss, or 0.420 per cent.; average 0.438 per cent. loss. According to the theoretical formula, no water of hydration should be found.

Sodium Content.—Sodium was determined by igniting a weighed portion of the material with sulphuric acid, followed by a small quantity of ammonium carbonate, heating the residue to low redness and weighing as sodium sulphate. Since lead was absent from the specimen of barbital-sodium Abbott no correction to the weight of sodium sulphate was necessary.

$Na_2SO_4 \times 0.3238 = Na$

Specimen A.—From 1.0605 gm. of material 0.3564 gm. of sodium sulphate was obtained, equivalent to 10.88 per cent. of sodium; a duplicate, weighing 1.6477 gm., gave 0.5489 gm. of sodium sulphate, equivalent to 10.75 per cent. of sodium; average 10.82 per cent. of sodium. Theory requires 11.17 per cent. of sodium.

Specimen B.—From 1.2019 gm. of material, 0.3961 gm. of sodium sulphate was obtained, equivalent to 10.67 per cent. of sodium. A duplicate of 1.1697 gm. of material gave 0.3854 gm. of sodium sulphate, equivalent to 10.67 per cent. of sodium; average 10.67 per cent. of sodium.

BARBITAL

A weighed quantity of the material (about 1 gm.) was dissolved in water, an excess of diluted hydrochloric acid added and the solution shaken with 25 c.c. of ether. The ether layer was removed, washed with 4 c.c. of water and the aqueous washings added to the aqueous solution. The shaking-out and washing process was repeated until extraction was complete, using 20 c.c. of ether for each shaking and 4 c.c. of water for each washing. The ether fractions were united, the mixture was allowed to evaporate spontaneously, the residue was dried over sulphuric acid and weighed.

Specimen A.—From 1.1279 gm. of material 0.9846 gm. of barbital was obtained, equivalent to 87.30 per cent. A duplicate of 1.0006 gm. of material gave 0.8739 gm. of barbital, or 87.33 per cent.; average, 87.31 per cent. of barbital. Theory requires a yield of about 89.33 per cent. of barbital from barbital sodium. The separated barbital melted at 188-9 C. (uncorrected).

Specimen B.—A weight of 1.0049 gm. of material gave 0.8837 gm. of barbital, or 87.94 per cent. A duplicate of 1.0042 gm. of material gave 0.8758 gm. of barbital, or 87.21 per cent.; average 87.57 per cent. of barbital. The barbital separated as above melted at 188-9 C. (uncorrected).

MEDINAL

The methods used in the examination of medinal were the same as those used in the analysis of barbital-sodium. Lead was present but the amount was so small that a correction to the weight of sodium sulphate in the sodium determination was not made. Owing to the small quantity of material available, duplicate determinations were not made on the specimen sent by the manufacturer.

Loss on Drying.—On drying at 120 C., 1.0016 gm. of Specimen A lost 0.0016 gm. or 0.16 per cent.

Sodium.—From 1.0484 gm. of material (Specimen A) 0.3574 gm. of sodium sulphate was obtained, equivalent to 11.04 per cent. of sodium. Theory requires 11.16 per cent. of sodium in barbital-sodium.

Barbital.—From 1.0016 gm. of material (Specimen A) 0.8894 gm. of barbital was obtained, equivalent to 88.80 per cent. Theory requires 89.33 per cent. of barbital in barbital-sodium.

Loss on Drying.—From 1.0003 gm. of Specimen B a loss of 0.0030 gm. was noted, or 0.30 per cent.; a duplicate of 1.6028 gm. gave 0.0058 gm. loss, or 0.36 per cent.; average 0.33 per cent.

Sodium.—A weight of 2.0031 gm. of material (Specimen B) gave 0.6778 gm. of sodium sulphate (without correction for traces of lead), or 10.95 per cent. of sodium.

Barbital.—From 1.0003 gm. of material (Specimen B), 0.8847 gm. of barbital was obtained, or 88.44 per cent.; a duplicate of 1.6028 gm. of material gave 1.4235 gm. of barbital, equivalent to 88.81 per cent.; average, 88.63 per cent. of barbital.

Lead.—Lead was determined as described below for the estimation of lead under veronal-sodium. From 15 gm. of material 0.0018 gm. of lead sulphate was obtained, equivalent to 0.01 per cent. of lead carbonate, $PbCO_3Pb(OH)_2$. This quantity is insufficient to respond to the U. S. P. test for heavy metals as described under sodium salicylate.

VERONAL-SODIUM WINTHROP

The methods used were the same as those used for barbital sodium, except that for lead which is described in detail in the paragraph below relating to that determination.

Loss on Drying at 120 C.—From 1.0416 gm. of material, a loss of 0.0031 gm. was noted, equivalent to 0.30 per cent. A duplicate of 1.017 gm. lost 0.0028 gm., or 0.28 per cent.; average 0.29 per cent. loss at 120 C.

Lead.—A weighed quantity of the material was dissolved in water so far as possible and the mixture (without filtration) saturated with hydrogen sulphid. After standing over night the precipitated lead sulphid was collected on a filter, the filter treated with diluted nitric acid containing a little hydrochloric acid, the solution evaporated in presence of sulphuric acid until white fumes appeared, 25 c.c. of 25 per cent. alcohol were added, the mixture was allowed to stand over night, the precipitated lead sulphate collected in a Gooch crucible, washed with 25 per cent. alcohol, dried at 120 C. and weighed.

$$PbSO_4 \times 0.85246 = (PbCO_3)_2Pb(OH)_2.$$

From 10.2080 gm. of material, 0.0577 gm. of lead sulphate was obtained, equivalent to 0.482 per cent. of basic lead carbonate $(PbCO_3)_2\ Pb(OH)_2$. A duplicate of 12.0111 gm. gave 0.0709 gm. of lead sulphate, equivalent to 0.503 per cent. of basic lead carbonate; average, 0.49 per cent. of basic lead carbonate.

Sodium.—Sodium had been determined by heating with sulphuric acid and weighing as sodium sulphate before the presence of lead was discovered. The results for sodium were found to be too high for theory. After the presence of lead had been demonstrated and its quantity determined, a correction was applied to the values for sodium. Since the presence of lead in the material augments the weight of sodium sulphate, the weight of lead sulphate produced by the lead in 1 gm. of material was calculated. This was found to be 0.00575 gm. From 1.0052 gm. of material 0.3496 gm. of sodium sulphate (containing a little lead sulphate) was obtained. A duplicate of 1.0032 gm. of the material gave 0.3514 gm. of impure sodium sulphate. The mean weight of impure sodium sulphate produced by 1 gm. of the material is 0.34903 gm. Subtracting 0.00575 gm. from this, a remainder of 0.34328 gm. of sodium sulphate remains. This is equivalent to 0.112154 gm. of sodium, or 11.21 per cent. Theory requires 11.16 per cent. of sodium in veronal-sodium.

Barbital (*Veronal*).—This was determined as described under barbital-sodium. From 1.0416 gm. of the material, 0.9238 gm. of barbital was obtained, equivalent to 88.69 per cent. A duplicate of 1.0012 gm. gave 0.8830 gm. of barbital, or 88.19 per cent.; average 88.44 per cent. of barbital. Theoretically veronal-sodium should produce 89.33 per cent. of barbital.

Loss on Drying (*Specimen B*).—A weight of 2.0029 gm. lost 0.0152 gm., or 0.759 per cent.; a duplicate of 1.0018 gm. lost 0.0068 gm., or 0.679 per cent.; average, 0.73 per cent. of loss on drying.

Sodium.—A weight of 1.0058 gm. gave 0.3357 gm. of sodium sulphate, equivalent to 10.88 per cent. of sodium; a duplicate of 2.0056 gm. gave 0.6789 gm. of sodium sulphate, equivalent to 10.96 per cent. of sodium; average 10.92 per cent. of sodium.

Total Barbital.—A weight of 1.001 gm. gave 0.8894 gm. of barbital, or 88.78 per cent. This includes both combined and uncombined barbital.

Uncombined Barbital.—This was determined by percolating a weighed quantity of the air-dried material with ether, expelling the solvent by evaporation, drying the residue over sulphuric acid and weighing. A weight of 10 gm. of material gave 0.0992 gm. of ether extract, equivalent to 0.992 per cent. of uncombined barbital. A duplicate of 20 gm. gave 0.1872 gm. of ether extract or 0.936 per cent.; average, 0.96 per cent. of uncombined barbital.

Heavy Metals (Specimen B).—A quantity of the material (about 1 gm.) was dissolved in 100 c.c. of water, the solution slightly acidulated with hydrochloric acid, warmed and saturated with hydrogen sulphid. No precipitate was given.

THE EXAMINATION OF LUMINAL AND LUMINAL-SODIUM

L. E. Warren, Ph.C., B.S.

Luminal is phenyl-ethyl-barbituric acid. The substance was described in N. N. R. 1919 under the name of phenobarbital. Phenobarbital differs from barbital only in the substitution of one ethyl group in the latter by a phenyl group. Phenobarbital is sold under the protected name "luminal," and the soluble salt, phenobarbital-sodium, is known as "luminal-sodium." Formerly both products were manufactured in Germany and each was formerly described in New and Nonofficial Remedies. During the World War the supplies of luminal and luminal-sodium in the United States became exhausted and for that reason both substances were deleted from New and Nonofficial Remedies.

Some time after the signing of the armistice the manufacture of these products was undertaken in this country and specimens each of luminal and of luminal-sodium of American manufacture were submitted to the Council on Pharmacy and Chemistry for inclusion with New and Nonofficial

Remedies. The products were manufactured by the Winthrop Chemical Co. of New York.

Each specimen was subjected to the tests for the respective product as described in New and Nonofficial Remedies 1919, supplemented by such other tests as experience and increased knowledge appeared to warrant, and each specimen was compared with a corresponding specimen that had been in stock for six years.

Luminal.—The specimen recently submitted corresponded to the description for phenobarbital as given in New and Nonofficial Remedies 1919, except that its melting point was 171-172 C., instead of 173-174 C. as stated in New and Nonofficial Remedies. The old specimen of luminal melted at 171-172 C. The melting point given in the literature for luminal is 172 C. In other respects the specimen compared favorably with the old specimen.

Based partly on the descriptions for luminal in the literature and partly on the results obtained in the examination, the following tentative description for luminal has been prepared:

> Luminal is a white, odorless, slightly bitter powder. It is very slightly soluble in cold water; slightly soluble in hot water; soluble in alcohol, ether and chloroform, and in alkaline solutions. It crystallizes from boiling water in lustrous leaflets and is precipitated unchanged by acids from its alkaline solutions. An aqueous solution of luminal has an acid reaction to litmus.
>
> Luminal melts not below 172 C.
>
> Shake about 0.3 gm. of luminal for a short time with 1 c.c. of normal sodium hydroxid and 5 c.c. of water and filter the mixture. Divide the filtrate into two portions and add mercuric chlorid test solution to one and silver nitrate test solution to the other. A white precipitate is given in each case.
>
> Boil about 1 gm. of luminal for five minutes in 10 c.c. of a 50 per cent. solution of sodium hydroxid. Ammonia is evolved.
>
> Dissolve about 1 gm. of luminal in 5 c.c. of normal sodium hydroxid and heat the solution for four hours on a boiling water bath, replacing the evaporated water from time to time. Crystals of phenyl-ethyl-acetyl urea separate on cooling. After recrystallization from dilute alcohol this substance melts at 147 C.
>
> Dissolve about 0.1 gm. of luminal in 1 c.c. of concentrated sulphuric acid. The solution is colorless.
>
> Incinerate about 0.5 gm. of luminal, accurately weighed. The ash amounts to not more than 1 per cent.

Luminal-Sodium.—The specimen of luminal sodium submitted was a white, finely granular, hygroscopic, odorless powder. It was very soluble in water; also soluble in alcohol, 1 gm. requiring somewhat less than 20 c.c. for solution. In this respect luminal-sodium differs very markedly from veronal-sodium, 1 gm. of which requires approximately 575 c.c. of alcohol for solution.

A portion of the specimen was heated for several hours with a 50 per cent. solution of sodium hydroxid. The resulting crystals were recrystallized from 50 per cent. alcohol and the melting point was found to be 147 C. This corresponds to phenyl-ethyl-acetyl urea, a compound formed when luminal or luminal-sodium is heated with sodium hydroxid.

On drying the recently submitted specimen of luminal sodium over sulphuric acid a loss of about 0.9 per cent. was found; on drying at 140 C. the loss was 4.26 per cent. An old specimen of luminal-sodium that had been in stock for six years lost 2.67 per cent. over sulphuric acid and 4.11 per cent. at 140 C. Another old specimen (Merck brand) lost 0.62 per cent. over sulphuric acid and 1.94 per cent. at 140 C. It is not clear whether the greater loss at 140 C. is due to water of hydration that the sulphuric acid failed to abstract or to decomposition of the product.[1]

On acidifying the aqueous solution (of the recently submitted specimen), shaking with ether, and evaporating the solvent, a residue of phenobarbital was given corresponding to 86.94 per cent. of the weight of substance taken. A duplicate gave 86.53 per cent. According to theory anhydrous phenobarbital-sodium should yield 91.34 per cent. of phenobarbital. One of the old specimens gave 86.98 per cent. and the other 85.72 per cent. of phenobarbital. The melting point of the separated phenobarbital from each specimen was 172 C.

Sodium was determined as sodium sulphate by evaporating the acid solution from which the phenobarbital had been extracted and heating the residue with sulphuric acid, a little ammonium carbonate being added before the final heating. The specimen of luminal-sodium recently submitted yielded sodium sulphate equivalent to 8.55 per cent. of sodium. One old specimen of luminal-sodium gave 8.55 per cent. of sodium and the other 8.56 per cent. Anhydrous phenobarbital-sodium should contain 9.05 per cent. of sodium.

The analytical evidence indicates that the composition of the market supply of luminal-sodium conforms more nearly to a salt having the formula $NaC_{12}H_{11}N_2O_3+\frac{1}{2}H_2O$ than to a salt containing no water of hydration. This may be seen by a glance at the accompanying table.

---

[1] The fact that the melting point of the phenobarbital extracted from the substance which has been heated is normal is indicative against the theory of decomposition.

ANALYSIS OF LUMINAL-SODIUM

Brand	Loss over H_2SO_4, per cent.	Loss at 140 C., per cent.	Pheno-barbital, per cent.	Sodium, per cent.	Total (as dried over H_2SO_4) per cent.	Total (as dried at 140 C.) per cent.
Winthrop.......	0.898	.....	86.94}86.74	8.67	96.51	.....
		4.26	86.53}	8.46	.....	99.25
Farbenfabriken	2.67	.....	87.03}86.98	8.54	98.24	.....
		4.106	86.94}	8.56	.....	99.61
Merck (old).....	0.615	1.94	85.72	8.56	94.89	96.22
Theory (anhydrous salt)	.....	.....	91.34	9.05	100.39	100.39
Theory......... ($NaC_{12}H_{11}N_2O_3+\frac{1}{2}H_2O$)	(3.424)	3.424	88.215	8.741	(100.38)	100.38

In view of the findings obtained in the analysis the following tentative description and standards for luminal-sodium were proposed:

> Luminal-sodium is a white, hygroscopic powder; very soluble in water; soluble in alcohol; practically insoluble in ether and chloroform. An aqueous solution of luminal-sodium has an alkaline reaction to litmus. On long standing or prolonged boiling of the aqueous solution 1 molecule of carbon dioxid is liberated and phenylethylacetyl urea is precipitated; after recrystallization from dilute alcohol this substance melts at 147 C.
>
> Incinerate about 0.5 gm. of luminal-sodium. The residue responds to tests for sodium carbonate.
>
> One gm. of luminal-sodium dissolves without residue in 20 c.c. of alcohol (distinction from barbital-sodium, which requires more than 500 c.c. of alcohol for solution).
>
> Dry about 1 gm. of luminal-sodium, accurately weighed, to constant weight over sulphuric acid. The loss does not exceed 5 per cent.
>
> Dissolve about 1 gm. of luminal-sodium, accurately weighed, in water; acidify the solution with sulphuric acid, shake the solution with successive portions of ether, allow the solvent to evaporate spontaneously, dry the residue to constant weight at 80 C. and weigh. The residue amounts to not less than 86 per cent. of the weight taken. The residue responds to tests for luminal (which see).
>
> Add 5 c.c. of dilute sulphuric acid to the aqueous solution remaininig from the preceding determination, evaporate the solution in a weighed platinum dish on a water bath, heat cautiously until the excess of sulphuric acid has been volatilized, add about 0.5 gm. of ammonium carbonate and heat to constant weight. The weight of sodium sulphate obtained corresponds to not less than 8.5 per cent. of sodium.
>
> $$Na_2SO_4 \times 0.3238 = Na.$$

BARIUM SULPHATE FOR ROENTGEN-RAY WORK

A. H. Clark, Ph.G., Sc.B.

Barium sulphate has to a high degree the property of obstructing the passage of the roentgen-ray and on this account it has come into quite general use in fluoroscopic examinations of the stomach and intestine. For this purpose large amounts must be given. Because of the extreme insolubility of barium sulphate in all of the gastro-intestinal fluids it is practically harmless if pure. Soluble salts of barium are very poisonous. This has been shown by the Bureau of Plant Industry of the U. S. Department of Agriculture, in its investigations into the causes of "loco weed disease" in domestic animals. At one time the cause of this disease was attributed to the presence of barium in the plants eaten as food by the animals. Barium salts are present in certain soils, and are absorbed by the plants.

Because of the high toxicity of the soluble barium salts it is very important that barium sulphate for roentgenographic work be free from soluble barium compounds, or from any barium compound likely to be soluble in the gastro-intestinal fluids.

Barium sulphate has been described in New and Nonofficial Remedies for several years. Tests intended to guard against the presence of harmful impurities are given in N. N. R. During the past year some modifications of these tests have been suggested by manufacturers. Other considerations also seemed to warrant further study of the standards for barium sulphate. The results of this work are given herewith.

Soluble Barium Compounds.—New and Nonofficial Remedies 1919 directs that 10 gm. of barium sulphate be boiled with 10 c.c. of acetic acid, specific gravity 1.064, and 90 c.c. of water. The mixture is filtered and 50 c.c. of the filtrate evaporated; to the residue are added 20 c.c. of water; the insoluble matter is removed by filtration and sulphuric acid added to the filtrate. No precipitate should appear within one half hour.

Half of the remaining acetic acid filtrate (25 c.c.) is tested for heavy metals by hydrogen sulphid.

Several points worthy of attention in this test were noted.

1. What strength of acetic acid is intended? Acetic acid of sp. gr. 1.064 might mean 90 per cent. or 62 per cent. strength.

2. The test does not take into consideration the nature of the soluble matter other than soluble barium salts or heavy metals.

3. The test does not consider the quantity of soluble matter. From 2 and 3 it may be noted that a considerable amount of calcium sulphate might be present and escape detection except that an undue amount of residue might excite suspicion.

As to the first query, experiments were conducted with 62 per cent. and with 90 per cent. acetic acid. The weights of residue obtained from portions of the same specimen of barium sulphate were practically the same in each case. Since the U. S. P. diluted acetic acid is 6 per cent. it is recommended that this strength of acid be directed to be used in this test.

ANALYSIS OF BARIUM SULPHATE

Brand	N. N. R. Method Residue (Grams)	Modified but 6 per Cent. Acid Residue (Grams)	Modified but 10 per Cent. Acid Residue (Grams)
Merck	0.0267	0.0317	......
Squibb	0.0110	0.0117	......
Brady	0.0048	0.0035	0.0032
Unknown	0.0072	0.0077	0.0057

Query No. 2.—In three out of four samples examined the soluble matter was found to be a calcium salt. Heavy metals were absent in all cases. This suggested the possibility of even larger amounts of calcium salts being present.

Query No. 3.—Since, as shown under No. 2, a calcium compound was present (other compounds might have been present) a quantitative statement as to the amount of soluble matter permitted seems desirable. If the test be carried out as directed in N. N. R. 1919, the 50 c.c. of filtrate would not represent 5 gm. of barium sulphate since a considerable loss of acetic acid is sustained in the boiling and the filtration. To avoid this, 10 gm. of barium sulphate were successively boiled with small amounts of the diluted acetic acid, the solution decanted to a filter after each treatment until the filtrate measured 100 c.c. Of this solution 50 c.c. then contained the soluble matter originally in 5 gm. of barium sulphate. The results by both methods are found in the table given herewith. Specimens of barium sulphate of the Merck, Squibb, and Brady brands and one of unknown manufacture were examined.

As a result of this examination it is suggested that the test for soluble salts in barium sulphate be made to read as follows:

> Boil 10 gm. of barium sulphate for roentgenographic work successively with several small portions of diluted acetic acid, decanting through a filter each time until a filtrate measuring 100 c.c. is obtained. Evaporate 50 c.c. of this filtrate to dryness on a water bath. The residue does not exceed 0.010 gm. (0.2 per cent.). After solution in water this residue gives no precipitate with a drop of diluted sulphuric acid on standing one hour (*barium*). The remaining acetic acid solution shows no cloudiness or coloration after saturation with hydrogen sulphid (*heavy meals*).

Phosphate.—The test for phosphate as described in N. N. R. 1919 has been criticized on the following grounds:

1. The strength of the nitric acid used is given in terms of specific gravity.
2. The directions to boil "for a few minutes" is indefinite.
3. The quantity of ammonium molybdate solution to be used is not stated.
4. No directions are given to heat the solution after adding the molybdate solution.

It was thought that the following procedure would remove all these objections and, since all the specimens were found free from phosphate when thus treated, the following modifications are recommended for inclusion in N. N. R.

> To 2 gm. of barium sulphate for roentgenographic work add 10 c.c. of 25 per cent. nitric acid and heat the mixture on a water bath for ten minutes. Filter the mixture, add 10 c.c. of ammonium molybdate solution to the clear filtrate and heat nearly to boiling. No yellow precipitate should appear on standing a half hour (*phosphate*).

Arsenic.—The test for arsenic has been criticized in that the strength of the stannous chlorid solution is not specified. To make this test conform to the U. S. P. procedure the following was suggested:

> Triturate 2 gm. of barium sulphate for roentgenographic work with 5 c.c. of concentrated hydrochloric acid. Add 10 c.c. of a saturated solution of stannous chlorid in hydrochloric acid. No darkening should take place within an hour (*arsenic*).

While conducting the foregoing tests it was noticed that the Brady sample was markedly different from the others in physical character. In the test for soluble barium compounds the material settled out in a compact mass, the others seemingly being much lighter or bulkier. This suggested the question as to what extent the physical condition of barium sulphate would effect its value in roentgenographic work. Time did not permit of any investigation along this line, but the point is made here in the hope that it may be taken up in the future, either in this Laboratory or by others interested in the subject.

BENZYL BENZOATE

Benzyl benzoate has come into prominence as an antispasmodic mainly because of the work of Macht[1] which was begun in 1916. Benzyl benzoate was first submitted to the Council on Pharmacy and Chemistry in 1919 by Hynson, Westcott & Dunning and, after the investigations of the standards by the Laboratory, it was first accepted for the 1919 edition of New and Nonofficial Remedies.

In the attempt to formulate standards the literature was first consulted for the physical constants of benzyl benzoate. At once difficulties were encountered from the fact that authorities generally agreed that below 20 C. benzyl benzoate is crystalline. At ordinary summer or room temperatures it is liquid. Constants were found for both phases, which were quite generally those given by Beilstein,[2] namely, M. P. below 20 C.; B. P. of crystals 345; B. P. of liquid 323-324 C.; Sp. Gr. at 18.5 C., 1.114. It is not stated whether the temperatures are corrected or uncorrected. It is also presumed that these constants are for a pure substance. No tests for identity and purity could be found in the literature.

All the samples examined were liquid and a temperature somewhat lower than 20 C. was required to solidify each of them. The boiling point of benzyl benzoate should be that for the liquid phase substance, or about 323-324 C. The uncorrected boiling point was found to be lower than this in every case but, by applying the proper correction, the corrected value was found to be very near that given above.

Some difficulty was experienced in determining the boiling point. The procedure that seemed to give the best results was that of the U. S. P. IX, a small flask placed over a hole in a piece of asbestos board being used, the latter being about 3/16 inch thick. The thermometer was protected from outside heating by covering the neck of the flask with asbestos sheeting. By rapid heating in this apparatus, very little decomposition of the product was noted in most of the samples examined. Disregarding the first 5 to 10 drops passing over, fully 95 per cent. could be distilled without marked decomposition or elevation of temperature. Because of these difficulties, and in view of the fact that only a purity of 95 per cent. for benzyl benzoate was required, some latitude in boiling point was allowed and a B. P. of 320-325 C. was agreed upon.

---

[1] Macht: J. Pharmacol. & Exper. Therap. **60**: 197, 1916.
[2] Beilstein: Organische Chemie, **2**, 1143.

The specific gravity was taken at 25 C., using a picnometer. The results are found in the table.

Since there was some uncertainty concerning the physical constants for benzyl benzoate, other tests were deemed necessary to insure a product of sufficient purity for medicinal use. Also simple tests for the identity of the substance were devised.

Since benzyl benzoate is the benzyl alcohol ester of benzoic acid it should readily saponify with caustic alkali, the products being benzyl alcohol and a benzoate. Benzyl alcohol may be separated from the saponified product by extraction with ether. After acidulating the residual solution the benzoic acid may be obtained in the same way. Each may be identified by its physical constants. The identity of benzoic acid may be confirmed by the characteristics of its ferric salt. If warmed with potassium permanganate, benzyl alcohol is oxidized and the peculiar odor of benzaldehyde is observable. These tests were considered sufficient for the identification of benzyl benzoate.

Pure benzyl benzoate leaves no residue on heating. None of the samples left a weighable residue. A limit of ash was therefore established.

Since hydrolysis of benzyl benzoate results in the production of free benzoic acid, a test for free acid in the product for medicinal use was thought desirable. All samples examined were neutral to dry litmus paper. With moistened litmus paper some differences were noted, the reaction being neutral in the case of two of three samples of one brand, doubtful in two others, and possibly acid in another. This test will be studied further as more samples are examined.

Since use is made of various chlorin compounds in some methods of manufacture of benzyl benzoate, the presence of these products should be guarded against. By applying the U. S. P. method for the detection of chlorination products in benzoic acid only one sample gave a positive reaction. It was thought that freedom from chlorin by this test would not be a severe requirement. The faults and limitations of this test are well known, but in the absence of a better procedure it was used.

Benzyl benzoate was found to be optically inactive.

On saponification, one gram molecule of benzyl benzoate requires two liters of half-normal potassium hydroxid. Each c.c. of half-normal alkali is then equivalent to 0.0106 gm. of benzyl benzoate and each gram of benzyl benzoate requires 9.43 c.c. of half-normal potassium hydroxid. Heating under a reflux condenser for two hours was found to be ample for saponification.

No objection was raised to a standard of not less than 95 per cent. of ester as determined by saponification, and but one sample being below this figure, it was adopted as the standard.

The analytical results obtained for the various samples are given in the appended table. The details of each test as finally adopted are found in the accompanying monograph which is that from New and Nonofficial Remedies 1920.

ANALYSIS OF BENZYL BENZOATE

	Color	B. P. Cor.	Sp. Gr. 25/25	Residue	Chlorin Comp.	Reaction to Dry Litmus Paper	Reaction to Wet Litmus Paper	Percentage of Ester by Saponification
H. W. D. & Co.	Very faint straw	323	1.1119	None	Present	Neutral	Very slightly acid	95.00
Van Dyk & Co.								
A	Colorless	325	1.1141	None	Absent	Neutral	Neutral	95.00
B	Colorless	323	1.1160	None	Absent	Neutral	Neutral	96.72
C	Colorless	320	1.1073	None	Absent	Neutral	Doubtful	87.30
D	Colorless	323	1.1155	None	Absent	Neutral	Doubtful	97.20

Based upon this work the following description of benzyl benzoate was prepared:

Benzyl Benzoate.—Benzylis Benzoas.—$C_6H_5COO.CH_2C_6H_5$.—The benzyl alcohol ester of benzoic acid. It contains not less than 95 per cent. of benzyl benzoate.

Benzyl benzoate is a colorless, oily liquid, above about 20 C. It is odorless, or has a faint aromatic odor, and a sharp, burning taste. It is insoluble in water or glycerin but is miscible in all proportions with alcohol, chloroform and ether.

Benzyl benzoate boils at 320 to 325 C. (corrected) with partial decomposition. When ignited it burns with a very smoky flame.

Specific gravity 1.09 to 1.13 at 15 C.; 1.083 to 1.122 at 25 C.

Benzyl benzoate is neutral to litmus. It is readily saponified by an alcoholic solution of potassium hydroxid. The solution obtained, when neutralized, yields a flesh-colored precipitate with ferric chlorid solution and, upon acidulation, a white, crystalline precipitate of benzoic acid separates. This precipitate may be identified by extracting with ether and applying the usual tests for benzoic acid.

Ten c.c. of benzyl benzoate should leave no weighable residue on evaporation and heating until all carbon is burned away.

To about 2 gm. of benzyl benzoate, accurately weighed, add 25 c.c. of a half-normal alcoholic potassium hydroxid and heat the mixture to incipient boiling under a reflux condenser for one hour. To the cooled solution add phenolphthalein and titrate the excess potassium hydroxid with half-normal hydrochloric acid. The volume of half-normal potassium hydroxid consumed should indicate not less than 95 per cent. of benzyl benzoate (each gm. of benzyl benzoate requires for saponification not less than 8.9 c.c. nor more than 9.4 c.c. of half-normal alcoholic potassium hydroxid).

THE EXAMINATION OF AMERICAN-MADE CHINOSOL

Chinosol was examined by the Council on its own initiative and a report published in 1908.[1] At that time chinosol was claimed to be oxychinolin sulphate $(C_9H_7ON)_2H_2SO_4$, but it was found by the Association's chemists to be "a mixture or a double salt of potassium sulphate and oxychinolin sulphate." Later on, the product was submitted to the Council by the Parmele Pharmacal Company, the American agents for the European manufacturer. After its identity as oxychinolin sulphate without admixture with potassium sulphate had been determined and other conflicts with the Council's rules had been removed, the product was accepted for New and Nonofficial Remedies.[2]

During the European war chinosol became unobtainable and, on that account, the product was deleted from New and Nonofficial Remedies. After the close of hostilities the product was again submitted to the Council by the Parmele Pharmacal Co. The specimens at first received after the war were found to be mixtures of potassium sulphate and oxchinolin sulphate, but a specimen received later was found to be of the correct composition.

Details of Analysis

Ash (First Specimen).—A weighed quantity of the specimen (1.0674 gm.) gave 0.2158 gm. of ash, equivalent to 20.21 per cent.; a duplicate of 1.8978 gm. gave 0.365 gm. of ash, equivalent to 19.28 per cent.; average 19.75 per cent. of ash. Tests indicated that the ash consisted essentially of potassium sulphate.

---

[1] Chinosol, J. A. M. A. **50**: 293 (Jan. 25) 1908.

[2] Chinosol, Ibid. **54**: 1789 and 1801 (May 28) 1910.

Sulphate (First Specimen).—Sulphate was determined by precipitation with barium chlorid test solution and weighing the barium sulphate in the usual way. From 0.1876 gm. of material, 0.1381 gm. of barium sulphate was obtained, equivalent to 54.95 per cent of potassium sulphate. A duplicate of 0.208 gm. gave 0.1500 gm. of barium sulphate, equivalent to 53.83 per cent. of potassium sulphate.

According to the formula, $(C_9H_7ON)_2.K_2SO_4.H_2SO_4$, the compound should represent sulphate equivalent to 30.98 per cent. of potassium sulphate. Since the ash amounts to only 19.75 per cent., it is evident that the formula containing equimolecular weights of oxychinolin sulphate and potassium sulphate does not apply to this specimen of chinosol, as sold.

The melting point of the specimen could not be determined accurately. This is as would be expected from a mixture of an organic substance and an inorganic substance.

The manufacturers, having been informed of the findings of the A. M. A. Chemical Laboratory, submitted another specimen of chinosol. This specimen gave no ash and yielded a base which, after recrystallization, melted at 74 C. An aqueous solution of the specimen gave a green color with ferric chlorid test solution. On solution in water and precipitation with barium chlorid test solution, the specimen gave barium sulphate equivalent to about 97 per cent. of oxychinolin sulphate. The specimen contained 0.05 per cent. of substance insoluble in water.

Sulphate (Second Specimen).—From 1.0055 gm. of material, 0.5833 gm. of barium sulphate was obtained, equivalent to 97 per cent. of normal oxychinolin sulphate $(C_9H_7ON)_2.H_2SO_4$.

THE EXAMINATION OF APOTHESINE

A number of synthetic substances are known which possess the power of producing local anesthesia. Several of these are derivatives of amino-benzoic acid.[1] Chemically, the simplest of the local anesthetics is the ethyl ester of amino-benzoic acid, $C_6H_4.NH_2.COOC_2H_5$, which is sold as *benzocain.* Another slightly more complex substance is the methyl ester of hydroxy-amino-benzoic acid $C_6H_4.NH_2.OH.COOCH_3$, which is known as *new orthoform.* Still another, somewhat more complex, is the hydrochlorid of the amino benzoic acid ester of diethyl aminoethane, $HCl.(C_2H_5)_2N(CH)_2.CO_2C_6H_4$

---

[1] Einhorn and Heitz: München. med. Wchnschr. **44**: 931, 1897.

NH_2. This has found extensive use under the name of "procaine."[2] Other of the local anesthetics are derivatives of butane, propane or phenylic alcohol, variously combined with several organic acid radicals, such as benzoic, cinnamic or valeric acid. Clearly, the number of compounds theoretically possible by variance of these groups is very large. Virtually all of the synthetic local anesthetics in use are less toxic than cocain, although but few of them are devoid of toxicity.

In its study of the available supplies of local anesthetics the Council on Pharmacy and Chemistry of the American Medical Association included "apothesine," a synthetic substance manufactured by Parke, Davis & Co. Apothesine is the hydrochlorid of the cinnamic acid ester of diethyl amino propane, $C_6H_5.(CH)_2.CO_2(C_2H_5)_2N:(CH_2)_3HCl$. It differs from procain in being a cinnamic instead of a benzoic ester and in being a derivative of propane instead of ethane.

A specimen of apothesine was received from the manufacturer. The specimen examined was a white, coarsely granular, nonhygroscopic, ordorless powder. It was soluble in water, alcohol and chloroform. The aqueous solution of apothesine was clear and nearly colorless and was found to be neutral to litmus paper. The taste of the aqueous solution was faintly bitter.

The aqueous solution of apothesine (1 : 100) was found to give a white precipitate with mercuric chlorid test solution, mercuric potassium iodid test solution, potassium cadmium iodid solution, phosphotungstic acid test solution, sodium salicylate solution, and with alkaline cupric tartrate solution, the latter being amorphous; a reddish-brown precipitate with iodine test solution; a yellow precipitate with potassium dichromate test solution, gold chlorid test solution, platinum chlorid test solution, picric acid test solution and with bromine test solution, the latter being soluble by heat; a salmon-colored precipitate with palladium chlorid solution; a pale, salmon-colored precipitate with sodium nitroprusside solution; and an orange yellow precipitate with chromic acid solution.

A mixture of equal weights of apothesine and mercurous chlorid blackened when moistened with 50 per cent. alcohol. This distinguishes apothesine from benzocain, β-eucain, cycloform, propaesin, holocain and new orthoform, but does not distinguish it from alypin, cocain, procain, stovain or quinin and urea hydrochlorid, each of which darkens under similar treatment. The aqueous solution of apothesine does not give the diazo reaction, thus sharply differentiating it from benzocain and procain, but not distinguishing it from most other synthetic cocain substitutes.

---

[2] Procain is the name adopted by the Federal Trade Commission for the substance originally introduced as "novocaine."

As an aid to the identification of the synthetic cocain substitutes Gadamer[3] attaches some importance to the melting points of their picrates. Accordingly, apothesine picrate was prepared by precipitating an aqueous solution of apothesine with an aqueous solution of picric acid. The precipitate, which becomes crystalline on standing, was recrystallized once from hot water and dried over sulphuric acid. The melting point of the well-dried specimen was found to lie between 110.5 and 111.5 C.

The specimen of apothesine examined lost 0.17 per cent. of its weight on drying at 120 C. A determination of its chlorid content by precipitation with silver nitrate solution and weighing as silver chlorid gave 12.16 per cent., calculated as hydrochloric acid, HCl. For the anhydrous salt, theory requires 12.25 per cent. The base was determined by treating an aqueous solution of apothesine with sodium hydroxid solution, shaking with ether, allowing spontaneous evaporation of the solvent and drying the residue over sulphuric acid. The yield was 87.05 per cent. Theory requires 87.75 per cent. for the anhydrous salt. The manufacturer states that the melting point of apothesine is 137 C. The melting point of the specimen was determined and found to be 135 C. (uncorrected.)

From the results of the examination, it appears that the composition of apothesine is essentially as claimed.

The toxicity of apothesine has been determined by Eggleston and Hatcher,[4] who found it to be about three fourths as toxic as cocain and about twice as toxic as procain. A case of death following the administration of apothesine has been reported.[5]

Based principally on the results obtained in the analysis, but supplemented to some extent by information furnished in the printed matter distributed by the manufacturers, a tentative description of apothesine, which includes tests for identity and purity, was prepared. This is given herewith:

---

[3] Gadamer: Lehrbuch der chemischen Toxicologie.

[4] J. Pharmacol. & Exper. Therap. **13**: 443, 1919.

[5] J. A. M. A. **74**: 265, 1920.

Apothesine is the hydrochlorid of the cinnamic acid ester of diethyl amino propane, $C_6H_5.(CH)_2.CO_2.(C_2H_5)_2:N.(CH_2)_3.HCl. = C_{16}H_{23}O_2NHCl$.

Apothesine occurs in white masses which are composed of minute, colorless needles; odorless; taste faintly bitter but producing a sense of numbness on the tongue; permanent in the air. It is soluble in water, alcohol, acetone and chloroform; nearly insoluble in ether. Its aqueous solution is neutral to litmus paper. Aqueous solutions of apothesine produce precipitates with the alkaline hydroxids, and their carbonates (the precipitate formed with sodium bicarbonate is soluble in an excess of the reagent) and with the usual alkaloidal reagents.

Apothesine melts at 137 C.

An aqueous solution of apothesine gives a white precipitate with silver nitrate test solution which is insoluble in nitric acid.

A mixture of equal weights of apothesine and mercurous chlorid blackens on being moistened with 50 per cent. alcohol (*distinction from. benzocain, holocain, β-eucain or new orthoform*).

Dissolve about 0.1 gm. of apothesine in 5 c.c. of water, add 2 drops of diluted hydrochloric acid and 2 drops of sodium nitrite solution (10 per cent.) and mix with a solution of 0.2 gm. of β-naphthol in 10 c.c. of sodium hydroxid solution (10 per cent.). A white precipitate is formed (*distinction from benzocain, which gives a deep red solution containing a red precipitate, and from procain, which gives a scarlet precipitate*).

Add a few drops of gold chlorid test solution to an aqueous solution of apothesine (1: 100). A lemon-yellow precipitate is produced *(distinction from procain, which forms a brown precipitate)*.

Dissolve about 0.1 gm. of apothesine in 5 c.c. of water, add 3 drops of diluted sulphuric acid and 5 drops of potassium permanganate test solution. The violet color of the latter disappears immediately *(distinction from cocain, which gives a violet precipitate)*.

Dissolve 0.1 gm. of apothesine in 1 c.c. of sulphuric acid. The solution remains colorless (*organic impurities*).

Dissolve 0.1 gm. of apothesine in 10 c.c. of water and saturate the solution with hydrogen sulphid. No coloration or precipitation is produced (*salts of heavy metals*).

Incinerate about 0.5 gm. of apothesine, accurately weighed. Not more than 0.1 per cent. of residue remains.

ACIDOL AND ACIDOL-PEPSIN

For a number of years betain hydrochlorid has been described in New and Nonofficial Remedies. Betain is an alkaloid found in the root of the beet, *Beta vulgaris*. Betain is believed to be physiologically inert. When combined with hydrochloric acid as betain hydrochlorid the aqueous solution of the compound liberates hydrochloric acid. It is, therefore, a convenient method for administering hydrochloric acid. Theoretically betain hydrochlorid contains 23.8 per cent. of hydrochloric acid (HCl). Betain hydrochlorid was admitted to New and Nonofficial Remedies under the protected name of acidol. At the time of admission to New and Nonofficial Remedies 1910, acidol was examined in respect to its hydrochloric acid content. Specimens of "acidol-pepsin," a mixture of betain hydrochlorid and pepsin in the form of tablets, were also examined. The hydrochloric acid content of betain hydrochlorid was determined by direct titration with normal potassium hydroxid, phenolphthalein being used as indicator. The acid in 0.6513 gm. of material required 4.3 c.c. of normal potassium hydroxid, equivalent to 0.155574 gm. of hydrochloric acid, or 23.88 per cent. A duplicate of 1.3986 gm. required 9.1 c.c. of normal potassium hydroxid, equivalent to 0.329238 gm. of hydrochloric acid, or 23.54 per cent.; average, 23.71 per cent. of hydrochloric acid. (Theory = 23.74 per cent.) The hydrochloric acid in acidol was determined also by solution in water, precipitation with silver nitrate and weighing as silver chlorid in the usual way. From 0.3377 gm. of the material, 0.3126 gm. of silver chlorid was obtained, equivalent to 0.079478 gm. of hydrochloric acid, or 23.54 per cent. A duplicate of 0.4435 gm. of material gave 0.4132 gm. of silver chlorid, equivalent to 23.89 per cent.; average, 23.61 per cent. of hydrochloric acid.

The acidol-pepsin tablets were submitted in two strengths, viz.: "mild" and "strong." The "mild" tablets were stated to contain 0.2 gm. of pepsin and 0.05 gm. of acidol; the "strong" tablets were claimed to contain 0.1 gm. of pepsin and 0.4 gm. of acidol. The tablets were crushed in water and the liberated hydrochloric acid was titrated with tenth-normal potassium hydroxid. The acid in five of the "mild" tablets required 1.7 c.c. of tenth-normal potassium hydroxid, equivalent to 0.0615 gm. of hydrochloric acid or 103.4 per cent. of the calculated quantity. A duplicate required the same amount of normal alkali. The acid in three of the "strong" tablets required 7.65 c.c. of normal potassium hydroxid, equivalent to 0.092259 gm. of hydrochloric acid (HCl), or 96.9 per cent. of the claimed amount.

The proteolytic activity of the acidol-pepsin tablets was not determined at the time of their receipt in 1910.

During 1919 newly sent specimens of acidol-pepsin tablets were received by the Association's laboratory. The strengths of the tablets were claimed to be the same as those received in 1910. The acidity of the new tablets was determined by the method previously used. The acid from four of the "mild" tablets required 1.81 c.c. of normal potassium hydroxid, equivalent to 0.660107 gm. of hydrochloric acid, or about 139 per cent. of the amount claimed. A duplicate gave the same result. The acid from two of the "strong" tablets required 5.146 c.c. of normal potassium hydroxid, equivalent to 98.8 per cent. of theory.

As a matter of interest the acidity of the specimens of old tablets was again determined. During the interval between the first and second assay the tablets had been stored in the dark in the original glass tube containers. The acid in three of the "mild" tablets required 1.068 c.c. of normal potassium hydroxid, equivalent to 109.4 per cent. of theory. A duplicate of four tablets required 1.3735 c.c. of normal alkali, equivalent to 105.6 per cent. of theory; average, 107.5 per cent. of theory. The acid from five of the "strong" tablets required 10.107 c.c. of normal potassium hydroxid, equivalent to 93.02 per cent. of theory. A duplicate of four tablets required 9.818 c.c. of normal alkali, equivalent to 94.27 per cent. of theory.

The proteolytic activity of the new tablets was determined by the method given for pepsin in the U. S. P. of 1890.[1] By this method the activity of the "mild" tablets appeared to be from ten to twenty per cent. of the strength calculated from the quantity of pepsin of U. S. P. strength claimed to be present. The "strong" tablets appeared to be from eighty to ninety per cent. of the strength claimed. At the same time some of the tablets that had been received in 1909 were tested by the same method for their proteolytic activity. Both the "mild" and the "strong" tablets of the earlier date were found to be inert. These experiments indicate that the acidity of acidol-pepsin tablets is not essentially reduced by keeping for several years, while the proteolytic activity is destroyed.

SODIUM DI-OXIDE, DENTAL

A specimen of sodium peroxid sold under the name "sodium di-oxide, dental," was submitted by the manufacturers, the Roessler and Hasslacher Chemical Co. The preparation is stated to be of exceptional purity, assaying above 93 per cent. of sodium peroxid, and to contain only traces of impurities (for example, less than 0.006 per cent. of iron).

The preparation was a very pale-yellow, hygroscopic powder. Sulphates, chlorids and phosphates were not found by the usual tests carried out on a solution in a suitable dilute mineral acid, dilute sulphuric acid being used as the solvent, except in the test for sulphates, in which latter, diluted hydrochloric acid was used. The diphenylamin test for nitrates could not be employed directly on the solution of the material in diluted sulphuric acid, owing to the fact that the liberated hydrogen peroxid reacts to form a blue color with the reagent, similar to that produced by nitrates. The difficulty was overcome by adding just sufficient tenth-normal potassium permangante to produce a faint pink color, adding a drop of very dilute oxalic acid and warming. In this solution nitrates were tested for by the addition of diphenylamin test solution in the usual way. The result was negative. A control containing a trace of nitrate was carried out. The blue color at the line of contact between the reagent and the solution was very marked.

---

[1] Warren, L. E.: A Note on a Very Old Specimen of Pepsin Annual Reports of the Chemical Laboratory of the A. M. A., Vol. 12, 1919, p. 23.

Sodium Peroxide.—Sodium peroxid was determined by the following method:

> From 1 to 2 gm. of the material is weighed and slowly added to 950 c.c. of 1 per cent. sulphuric acid. The solution is made up to 1,000 c.c. and aliquot portions of 100 c.c. each taken for titration. Tenth-normal potassium permanganate is added from a buret until a faint pink color is obtained.
>
> One c.c. N-10 $KMnO_4$=0.0039 gm. of Na_2O_2.

In the assay 1.6724 gm. of the material was dissolved in diluted sulphuric acid (1 per cent.) to make 1,000 c.c. An aliquot portion of 100 c.c., representing 0.16724 gm. of material, required 40.11 c.c. of tenth-normal potassium permanganate, equivalent to 93.53 per cent. of sodium peroxid. A duplicate of 100 c.c. required the same quantity of tenth-normal potassium permanganate.

Sodium Hydroxid.—An attempt was made to estimate the sodium hydroxid content by calculation from the sodium peroxid and total sodium contents. Sodium was determined by evaporating a portion (250 c.c. of the solution used for the sodium peroxid determination) to dryness, heating to remove excess of sulphuric acid, heating with a small quantity of ammonium carbonate and weighing the residue of anhydrous sodium sulphate. The sodium in the sodium peroxid, the latter, as determined by titration, was calculated to anhydrous sodium sulphate. This was subtracted from the sodium sulphate found and the balance of sodium sulphate calculated to sodium hydroxid. From 250 c.c. of the solution, representing 0.4181 gm. of material, 0.7667 gm. of anhydrous sodium sulphate was obtained. A duplicate gave 0.7659 gm. of anhydrous sodium sulphate; average, 0.7663 gm. of anhydrous sodium sulphate, or 3.0652 gm. of anhydrous sodium sulphate for the entire sample.

93.53 per cent. of 1.6724 gm. = 1.56429 gm. absolute Na_2O_2 in sample.

1.56429 gm. of Na_2O_2 = 2.849398 gm. of Na_2SO_4.

3.0652 gm. of Na_2SO_4 — 2.849398 gm. of Na_2SO_4 = 0.2158 gm. of Na_2SO_4.

0.2158 gm. of Na_2SO_4 = 0.10525 gm. of NaOH, equivalent to 6.23 per cent.

According to the analysis, therefore, sodium di-oxide, dental, appears to be composed of about 93.5 per cent. of sodium peroxid and 6.25 per cent. of sodium hydroxid with an analytical error of 0.25 per cent.

RESTORIA

According to the label, "Restoria For Bad Blood" contains "alcohol 34 per cent." It is marketed by the "Restoria Chemical Company, Kansas City, Mo., U. S. A."

After agitation, Restoria is a dark colored, muddy looking liquid of a greenish cast, the clear portion on standing being of a dark, red-brown color. It has an odor like vegetable extractive and an intensely bitter taste. On standing a large quantity of amorphous matter settles out and a small quantity of a greenish, oily material (about 4 c.c. from 500 c.c. of sample) floats. The oily matter carries with it a flocculent, greenish solid.

When heated with nitric acid or strong sulphuric acid, iodin vapors are given off. A portion of Restoria filtered clear responds to the usual tests for iodids. When determined quantitatively and calculated to potassium iodid, the iodid corresponds to 1.6934 gm. of potassium iodid in 100 c.c.

After a moist combustion with sulphuric acid neither arsenic, mercury, nor other heavy metals could be detected. Potassium is present in the ash.

An intensely bitter, oil-like substance is obtained by extraction with ether from acid solution.

Extracted with chloroform from alkaline solution, a residue is obtained which gives decided alkaloidal reactions with iodin test solution, potassium mercuric iodid test solution, picric acid test solution, and phosphomolybdic acid test solution. This residue is only slightly bitter. It is yellow in color and not very soluble in ether.

In conclusion, "Restoria For Bad Blood" contains no mercury or arsenic, but does contain iodid, probably potassium iodid, much vegetable extractive, including some alkaloidal drug and a bitter oil or oleoresin.

THE RELATIVE PERMANENCY IN MOIST AIR OF PILOCARPIN HYDROCHLORID AND PILOCARPIN NITRATE

The United States Pharmacopeia IX describes pilocarpin hydrochlorid and pilocarpin nitrate. Since each salt is freely soluble in water and soluble in most other solvents in pharmaceutical practice, there appears to be no advantage in medicine for officializing both substances. The committee appointed by the Council on Pharmacy and Chemistry for the Revision of Useful Drugs decided to eliminate one of these salts from the next edition of that work.

Statements in the literature, including the United States Pharmacopeia, indicated that the nitrate is permanent in the air while the hydrochlorid is deliquescent. Unfortunately the recorded statements were not sufficiently definite to determine the extent of the deliquescence of the hydrochlorid, that is, whether the salt would become liquid in moist air or only slightly moist. A few experiments were undertaken to determine the facts.

Weighed portions each of freshly purchased specimens of pilocarpin hydrochlorid and pilocarpin nitrate were dried over sulphuric acid to constant weight. The dried specimens were then placed in a water-saturated atmosphere (a desiccator containing water instead of sulphuric acid) and the weights determined at intervals. Over sulphuric acid, pilocarpin hydrochlorid lost but little, the loss being only 0.2 per cent. in forty-eight hours. Over water, it steadily increased in weight so that it had become nearly completely liquefied in twelve hours and completely liquefied in thirty-six hours. Even after liquefaction had taken place the solution continued to take up water for a considerable time. The results obtained were as folltws: A weight of 0.7241 gm. of pilocarpin hydrochlorid lost 0.0009 gm. in forty-eight hours over sulphuric acid, or 0.12 per cent. The dried salt (0.7232 gm.) gained 0.1773 gm. in twelve hours over water, or 24.5 per cent.; in thirty-six hours the gain was 0.431 gm., or about 60 per cent. of the original weight. In 168 hours the gain was 0.9815 gm. or about 135 per cent. In 240 hours the gain was 1.1887 gm., or 164 per cent. In 808 hours the gain was 2.1042 gm., or 290.6 per cent.

Pilocarpin nitrate lost a very little of its weight over sulphuric acid, and the dried salt when placed over water gained less than the original loss over sulphuric acid. The results are as follows: A weight of 0.4578 gm. lost 0.0024 gm. in forty-eight hours over sulphuric acid, or 0.5 per cent. The dried salt (0.4555 gm.) gained 0.0021 gm. in 72 hours over water, or 0.45 per cent.

The experiments show that pilocarpin nitrate is practically stable in moist air and that the hydrochlorid is so deliquescent as to be seriously troublesome in pharmacy. Pilocarpin nitrate was, therefore, retained in Useful Drugs and the hydrochlorid eliminated. The retention of the hydrochlorid in the U. S. Pharmacopeia should be discouraged by pharmacists.

SAJODIN

In 1906, E. Fischer and J. V. Mering[1] described a new class of iodin preparations which were produced from certain monoiodo fatty acids of high molecular weight by combining them with calcium, strontium or magnesium. Of these the calcium salt of monoiodobehenic acid was found to be easily made and particularly well adapted to therapeutic uses. According to Zernick[2] monoiodobehenic acid had been described previously by Alexandroff and Saytzeff[3] who prepared it by the action of iodin and phosphorus on erucic acid, an unsaturated acid from rape-seed oil. The American agents of the original manufacturers of Sajodin state in a circular that it "arises from erucic acid of oil of rape-seed by the incorporation of HI."

Sajodin was first marketed in 1906 by Farbenfabriken, vorm. Friedr. Bayer & Co., Leverkusen, Germany, and Farbwerke, vorm. Meister Lucius and Bruening, Hoechst-am-Main, Germany. It was accepted for New and Nonofficial Remedies 1906, and the description appearing in N. N. R.

---

[1] Fischer and Mering: Med. Klin., 1906, 7.

[2] Arbeit aus dem Pharm. Inst. der Univ. Berlin, **4**: 62, 1907.

[3] J. Prakt. Chem. **49**: 58, 1894.

at that time was prepared from information furnished by the manufacturers, and from published statements. These statements were never challenged and therefore remained substantially the same in every edition of N. N. R. until the description was omitted in 1919, because the product was no longer on the market. The 1919 edition of N. N. R. was hardly out of press when the Winthrop Chemical Co., Inc., of New York submitted a sample of Sajodin which was said to be made in the United States. It seemed important, then, to check up the claims as to composition, purity, etc., which were made for the substance.

Erucic acid is an unsaturated acid having the formula $C_{22}H_{42}O_2$ and behenic acid a saturated acid having the formula $C_{22}H_{44}O_2$. Erucic acid should then absorb hydrogen iodid, HI, to form $C_{22}H_{43}IO_2$ or monoiodobehenic acid. Presumably this acid combined with calcium (calcium hydroxid?) gives the calcium salt, or Sajodin. If Sajodin be a normal calcium salt of monoiodobehenic acid, it must contain 26 per cent. of iodin and 4.1 per cent. of calcium, and yield an ash of 5.74 per cent. of calcium oxid.

The properties ascribed to Sajodin by the original manufacturers are: A colorless, odorless, and tasteless powder which is insoluble in water. If heated it gives off an abundance of iodin vapor and if exposed to light the superficial portion becomes yellow without material decomposition.

Zernick[4] examined Sajodin when it first appeared on the market in 1906. He found it to have the properties mentioned above but in addition stated that it was nearly insoluble in cold alcohol, and ether, and soluble in warm chloroform. He determined the moisture and the calcium content, and described a saponification method for determining the percentage of iodin. He also suggested that it should be free from soluble iodids, and other soluble salts.

As stated above, the Winthrop Chemical Co. of New York now manufacture Sajodin in the United States. This firm at first submitted tablets of Sajodin, and later the powdered substance, with a view of having the product described in New and Nonofficial Remedies. Along with the samples submitted by the Winthrop Co., there have been examined two samples of the original Sajodin, one from the files of the Chemical Laboratory, referred to in this report as "Bayer

---

[4] Arbeit aus dem Pharm. Inst. der Univ. Berlin, Vol. IV, 1907, p. 62.

A," the other supplied by Dr. Sollmann of Cleveland, and referred to as "Bayer B." The results of the examination made on these various samples have been tabulated and are shown in the accompanying table.

ANALYSES OF SAJODIN

Color	Solubility in Chloroform	Moisture, per cent.	Ash, per cent.	Iodin, Carius Method, per cent.	Iodin, Saponification Method, per cent.	Calcium, per cent.
Winthrop No. 1 colorless......	Soluble	1.59	6.43	22.45	21.29	4.4
Winthrop No. 2 pale yellow...	Soluble	1.66	6.06	.....	24.79	...
Bayer A, pale yellow.........	Soluble	1.75	6.37	.....	25.11	...
Bayer B, pale yellow.........	Soluble	1.95	6.29	.....	24.68	...

The chloroform solution of Sajodin was not perfectly clear in any of the specimens tested.

Based partly on the foregoing data and partly on information already embodied in N. N. R., the revised monograph for Sajodin as given below was prepared. This was accepted by the Winthrop Chemical Co.

Sajodin is a colorless or slightly yellow powder; odorless; tasteless; unctuous to the touch; insoluble in water; very slightly soluble in cold alcohol, and in ether, and freely soluble in warm chloroform. When heated it chars, gives off violet vapors of iodin and leaves a residue of calcium oxid.

Shake 0.5 gm. of Sajodin thoroughly with 10 c.c. of boiling water and filter. The filtrate is neutral to litmus (*calcium hydroxid*) and gives but a slight opalescence with silver nitrate solution (*soluble iodids*). Five c.c. of the filtrate, evaporated in a platinum dish gives no weighable residue (*soluble salts*).

Dissolve 0.5 gm. of Sajodin in 5 c.c. of warm chloroform. The solution is clear or but slightly opalescent and only a trace of solid matter separates within 2 hours.

Ignite 0.5 gm. of Sajodin. The residue dissolves completely in hydrochloric acid, and this solution, after being made alkaline with ammonia water, yields a precipitate on the addition of ammonium oxalate (*calcium*).

Strongly ignite about 0.5 gm. of Sajodin, accurately weighed. The ash amounts to not more than 6.2 per cent.

Dry about 1 gm. of Sajodin, accurately weighed, to constant weight at 100 C. The loss is not more than 2 per cent. (*limit of moisture*).

Thoroughly ignite an accurately weighed quantity (about 2 gm., previously dried at 100 C.). Extract the ash with hot, dilute hydrochloric acid. To the acid solution add ammonia water in slight excess, then an excess of ammonium oxalate solution, collect the precipitate, heat it to calcium oxid in the usual manner and weigh. The calcium amounts to not more than 4.2 per cent. of the weight taken.

To about 1 gm. of Sajodin dried at 100 C., accurately weighed, and contained in a 500 c.c. Ehrlenmeyer flask, add 50 c.c. of alcoholic potassium hydroxid. Heat the mixture for two hours under a reflux condenser. Remove the condenser, boil off the alcohol, taking care to avoid loss by bumping. Transfer the residue to a separator, using at first warm water but finally a little diluted nitric acid to insure complete transfer of the iodid to the separator. Cool the contents of the separator, add 50 c.c. of ether and sufficient diluted nitric acid to decompose the soap. If the solution becomes yellow from liberation of iodin, add a little sodium sulphite to reduce the iodin. Shake thoroughly and draw off the aqueous layer through a wet filter, into a 500 c.c. flask. Wash the ether in the separator with three separate portions of 25 c.c. each of water, adding these through the filter to the acid solution in the flask, the volume of which should now be about 200 c.c. Warm to expel dissolved ether, cool and add 5 c.c. of concentrated nitric acid and 25 c.c. of tenth-normal silver nitrate solution. Titrate the excess of silver salt with tenth-normal potassium sulphocyanate, using ferric ammonium sulphate as indicator. The volume of tenth-normal silver nitrate consumed indicates not less thain 24.5 per cent. of iodin. Each gram of Sajodin corresponds to not less than 19.3 c.c. of tenth-normal silver nitrate solution.

The iodin content of Sajodin may also be determined by the Carius method, about 0.5 gm. of Sajodin being used in the test.

Details of Analysis

Moisture (Loss on Drying at 100 C.).—Winthrop No. 1: A sample weighing 1.1455 gm. lost 0.0167 gm., or 1.46 per cent. In a duplicate test, 4.2793 gm. lost 0.0736 gm., or 1.72 per cent.; average, 1.59 per cent. Winthrop No. 2: A weight of 1.2927 gm. lost 0.0216 gm., or 1.67 per cent. In a duplicate, 1.0923 gm. lost 0.0182 gm., or 1.67 per cent. Another portion, weighing 1.1470 gm., lost 0.0190 gm., or 1.66 per cent. Another portion, 1.1440 gm., lost 0.0189 gm., or 1.65 per cent.; average, 1.66 per cent. of loss on drying. Bayer A: A weight of 3.0614 gm. lost 0.0535 gm., or 1.75 per cent. Bayer B: A weight of 2.8395 gm. lost 0.0556 gm., or 1.95 per cent.

Ash.—Winthrop No. 1: A weight of 0.7794 gm. left a residue of 0.0501 gm., or 6.43 per cent. Winthrop No. 2: A weight of 1.0853 gm. left a residue of 0.0658 gm., or 6.06 per cent. Bayer A: From 1.2168 gm. of material, a residue of 0.0775 gm. was obtained, equivalent to 6.37 per cent. Bayer B: A portion weighing 0.6122 gm. left a residue of 0.0385 gm., or 6.29 per cent.

Iodin.—Winthrop No. 1: A weight of 1.0035 gm. consumed 16.9 c.c. of tenth-normal silver nitrate. This indicates 0.2145 gm. of iodin, equivalent to 21.37 per cent. A duplicate of 1.0083 gm. consumed 16.84 c.c. of tenth-normal silver nitrate. This indicates 0.2137 gm. of iodin, equivalent to 21.2 per cent.; average, 21.29 per cent. of iodin. By the Carius method 0.4094 gm. gave 0.1695 gm. of silver iodid, equivalent to 0.0914 gm. of iodin, or 22.32 per cent. of iodin. A duplicate of 0.4032 gm. gave 0.1685 gm. of silver iodid, equivalent to 0.091 gm. of iodin, or 22.58 per cent. of iodin; average, 22.45 per cent. of iodin. Winthrop No. 2: A portion weighing 1.0741 gm.

consumed 21.1 c.c. of tenth-normal silver nitrate. This indicates 0.2678 gm. of iodin, equivalent to 24.93 per cent. A weight of 1.280 gm. consumed 21.9 c.c. of tenth-normal silver nitrate. This indicates 0.2779 gm. of iodin, or 24.64 per cent.; average, 24.79 per cent. of iodin. Bayer A: A weight of 0.8805 gm. consumed 17.42 c.c. of tenth-normal silver nitrate. This indicates 0.2211 gm. of iodin, equivalent to 25.11 per cent. Bayer B: A portion weighing 1.1269 gm. consumed 21.91 c.c. of tenth-normal silver nitrate. This indicates 0.2781 gm. of iodin, equivalent to 24.68 per cent.

Calcium.—Winthrop No. 1: A portion weighing 0.7794 gm. gave 0.0484 gm. of calcium oxid. This is equivalent to 0.0346 gm. of calcium, or 4.44 per cent. A duplicate of 0.9704 gm. gave 0.053 gm. of calcium oxid. This is equivalent to 0.0379 gm. of calcium, or 4.36 per cent.; average, 4.4 per cent. of calcium.

Sajodin Tablets.—It is stated by the manufacturers, the Winthrop Chemical Co., that Sajodin Tablets contain 8 grains (0.52 gm.) of Sajodin. Nothing further as to their composition is offered.

The tablets submitted were uncoated, white, odorless and tasteless. They were not entirely soluble in warm chloroform. On heating, vapors of iodin were given off.

The tablets weighed an average of 1.0485 gm. It is evident, therefore, that they contain considerable foreign matter, since only 0.52 gm. of Sajodin is claimed to be present. On examination with the microscope, a large portion of this foreign matter was seen to be corn starch. On ignition, considerable ash was obtained, a part of which was not soluble in hydrochloric acid.

The tablets were examined for soluble iodids and other soluble salts by the method given under Sajodin, except that cold water was used in place of hot water as there directed.

Extraction with warm chloroform showed that 51.9 per cent. of the tablets was soluble. One tablet, weighing 1.0452 gm., gave 0.5421 gm. of chloroform-soluble material.

The total ash amounted to 12.6 per cent. One tablet weighing 1.0535 gm., gave 0.1328 gm. of ash.

The total iodin by the Carius method amounted to 12.61 per cent. A weight of 0.5136 gm. gave 0.124 gm of silver iodid, indicating 0.06699 gm. of iodin, equivalent to 13.04 per cent. A duplicate of 0.5101 gm. gave 0.119 gm. of silver iodid, equivalent to 0.06429 gm. of iodin, or 12.28 per cent.; average, 12.61 per cent. of iodin.

Based on this examination and that of Sajodin, the following standards for Sajodin Tablets, 8 grains, have been prepared:

> Sajodin Tablets, 8 grains, when examined by the tests given under Sajodin, using cold water for extraction in place of hot water, should be free from soluble calcium salts, soluble iodids, and other soluble salts. Sajodin Tablets should respond to the tests for calcium.
>
> Not less than 0.52 gm. of substance from each tablet should be soluble in warm chloroform.
>
> If assayed by the methods given under Sajodin, the tablets should contain not less than 12.25 per cent. of iodin.

CURTIS' SACRED BARK ROOT AND HERB COMPOUND

This preparation is said to be put out by Hal A. Curtis, of Chicago, but his home address is said to be Glendale, California. A specimen of the preparation was examined. It was a dark brown liquid having an odor like a mixture of peppermint, sassafras and wintergreen ("artificial sarsaparilla") and a mawkish taste. Qualitative tests indicated the presence of sodium, a sulphate, caramel, alcohol, reducing sugars, extractives from an emodin-bearing drug (probably debitterized cascara) and small amounts of salicylate. Alkaloids, ammonium salts, arsenic, iodids, magnesium, mercury salts, saccharin and phenolphthalein were absent. From the examination, Curtis' Sacred Bark Root and Herb Compound appears to be a hydro-alcoholic solution of sodium sulphate (Glauber's salt) and glucose, colored with caramel and containing extractives from an emodin-bearing drug, probably cascara. It is preserved with small amounts of a salicylate, probably sodium salicylate (in addition to alcohol).

Details of Analysis

Sodium sulphate was determined by precipitation with barium chlorid solution and weighing as barium sulphate. The barium sulphate obtained was equivalent to 4.23 gm. of hydrated sodium sulphate ($Na_2SO_4.10H_2O$) per 100 c.c. This is equivalent to about 19¼ grains per fluidounce. The dose of the nostrum recommended is one tablespoonful, or ½ fluidounce. In this dose the patient would receive about 10 grains of sodium sulphate, or approximately about 1/24 of the U. S. P. dose of Glauber's salt.

Salicylic acid was determined approximately by acidifying a portion of the preparation with hydrochloric acid, shaking with ether until extraction was complete, shaking the united ether extracts with very dilute ammonia water, acidifying the ammonia solution, extracting the latter repeatedly with chloroform, evaporating the chloroform, drying the residue over sulphuric acid and weighing. The residue was slightly contaminated with emodin-like substances but did not appear to be seriously impure. The melting point was not taken, as the substance was identified by the ferric chlorid test and by precipitation with iodin in alkaline solution. It was not thought worth while to determine the salicylic acid by the iodin method.[1]

GUETH'S CANCER CURE

Inquiries were received concerning the composition of Gueth's Cancer Cure, put out by Frank Gueth of Hicksville, Ohio, and a specimen was sent by one of the correspondents. The specimen had an odor like acetic acid, a strong acid reaction to litmus, and appeared to contain some vegetable drug in suspension.

Acetic acid was identified by the odor, and by the dark red color which was given on adding a few drops of ferric chlorid test solution to a portion of the filtrate obtained by removing the solid matter from some of the preparation by filtration. Microscopic examination indicated the presence of powdered sanguinaria (blood root). The presence of blood root was confirmed by extraction of the mixture with ether, after making alkaline, and treatment of the ethereal solution with a drop of hydrochloric acid. A beautiful red precipitate was formed which settled out of the ether. A solution of this precipitate in water gave the usual reactions for alkaloids.

The examination indicates that the preparation consists essentially of a suspension of powdered sanguinaria (blood root) in acetic acid. Quantitative determinations were not made. Years ago blood root, because of its irritant properties, was thought by some to be of value in the treatment of cancer. It never attained much popularity with the medical profession and has long since fallen into disuse.

---

[1] J. of Assoc. Ag. Chem. **1**: 343, 1915.

IODEX AND LIQUID IODEX

The A. M. A. Chemical Laboratory examined Iodex in 1915.[1] The claims made, at that time, by the exploiters, Menley & James, were shown to be contrary to facts in that Iodex contained only traces of free iodin while they claimed "5 per cent. Therapeutically Free Iodin." Even the *total* quantity of iodin was shown to be only about one-half of the 5 per cent. claimed to be present as free iodin.

An examination of the advertising matter sent out by Menley & James in 1919 showed that substantially the same claims were being made as in 1915. This at once suggested the inquiry: Since the claims are the same as previously made, have the manufacturers altered the composition to conform to the claims? The answer is found in the results of the analysis of two samples purchased in the open market early in 1919.

This analysis shows conclusively that Iodex is essentially the same as in 1915, that is, that it contains no free iodin and only about three fifths of the total amount of iodin claimed.

It would seem that Iodex (Ung. Iodi., M. & J.) is in obvious conflict with Section 7 of the Food and Drugs Act. While it is sold under a name recognized by the U. S. Pharmacopeia, namely, Ung. Iodi., it does not conform to the standards of the U. S. Pharmacopeia for that product. Iodin ointment U. S. P. is made with 4 per cent. of free iodin, 4 per cent. of potassium iodid, 12 per cent. of glycerin, and a benzoinated lard base. It should then contain approximately 7 per cent. of total iodin. It has been shown by Warren[2] that about 75 per cent. of the iodin in the U. S. P. ointment remains in the free state even after months of standing. Ung. Iodi, U. S. P., then, should contain about 3 per cent. of free iodin. Iodex contains no free iodin, or but traces, and no potassium iodid. Furthermore, the Iodex label declares the presence of 5 per cent. of "therapeutically free" iodin. As a matter of fact, the amount of iodin is variable, the highest amount found being 3.5 per cent. and samples containing as low as 2.63 per cent. have been examined.

It would seem further that Iodex is misbranded under the Sherley amendment in that it is said that it "may be used externally with advantage in all cases where the action of iodine is desired." Since it contains no iodin *as such* this cannot possibly be true. It is also stated in a circular accompanying the trade package that "Thirty minutes after inunction iodin can be found in the urine." This statement has also been shown to be untrue (Annual Reports A. M. A. Chem. Lab., 1915, p. 89).

---

[1] Annual Reports of the Chem. Lab. of the A. M. A., 1915, p. 89.

[2] Warren, L. E.: Iodin Ointment, Am. J. Pharm. August, 1917, p. 339.

Details of Analysis

Iodex.—This is a rather soft ointment, almost black but with a decided greenish cast in thin layers. It is soluble in chloroform but is only partly saponified and dissolved by alcoholic potassium hydroxid. Iodex has a distinct odor like oleic acid.

Free Iodin.—When examined by the method previously used[3] only minute traces of free iodin were found.

Total Iodin.—The methods employed were as follows: 1. Iodex was saponified by boiling for from two to three hours with alcoholic potassium hydroxid. The alcohol was then evaporated and the iodin determined by the method described in the U. S. Pharmacopeia for thymol iodid.

2. The same as Method 1, except that after ignition of the saponified mixture the halogen was determined by weighing as silver iodid.

3. The Carius method.

It should be noted that Methods 2 and 3 determine chlorin and bromin should any be present with the iodin.

When 5 gm. of Sample 1 was assayed by Method 1, it required 73.56 c.c. of tenth-normal sodium thiosulphate, equivalent to 3.11 per cent. of iodin. In a duplicate, 2.7565 gm. of Iodex required 38 c.c. of tenth-normal sodium thiosulphate, equivalent to 2.92 per cent. of iodin; average of the two, 3.02 per cent. of iodin.

A weight of 2.5800 gm. of Sample 1, assayed by Method 2, gave 0.1582 gm. of silver halid, equivalent to 0.0855 gm. of iodin, or 3.31 per cent.

A weight of 0.588 gm. of Sample 2, assayed by the Carius method, gave 0.0388 gm. of silver halid, indicating 0.02096 gm. of iodin, or 3.52 per cent. In a duplicate, 0.5342 gm. gave 0.0338 gm. of silver halid, indicating 0.01826 gm. of iodin, or 3.42 per cent.; average, 3.49 per cent. of iodin.

---

[3] Ibid., p. 90.

Liquid Iodex.—This is sold by Menley & James, Ltd., the firm selling Iodex Ointment. According to a circular in a trade package "the valuable properties of Free Iodine are available in Liquid 'Iodex' in a state of greatly enhanced activity; but the irritating, corrosive and hardening drawbacks of ordinary solutions of the drug are absent." The label on a bottle reads as follows: "Liquid 'Iodex' (Liq. Iodi. M. & J.). A non irritant preparation of iodine (2½%) . . . This product contains Free Iodine. . . ."

The sample of Liquid Iodex purchased on the open market was found to be a reddish liquid with an odor like oleic acid. It dissolved completely in chloroform.

Free Iodin.—A weight of 6.2936 gm. was dissolved in chloroform and the solution shaken with 25 c.c. of a solution of potassium iodid. The iodin which passed into the potassium iodid solution was titrated with tenth-normal sodium thiosulphate, 0.81 c.c. being required. This indicates 0.01022 gm. of iodin, or 0.16 per cent.

Total Iodin.—Total iodin was determined by Method 1 as given above under Iodex. A weight of 4.466 gm. required 32.93 c.c. of tenth-normal sodium thiosulphate, equivalent to 0.06964 gm. of iodin, or 1.55 per cent. In a duplicate, 5 gm. of material required 33.3 c.c. of tenth-normal sodium thiosulphate, equivalent to 0.7043 gm. of iodin, or 1.41 per cent.; average, 1.48 per cent. of iodin.

Liquid Iodex, then, contains but little (0.16 per cent.) free iodin and only about three fifths of the total iodin claimed.

I. G. O.

I. G. O. is an iodin ointment. It is said to be made by Dr. H. S. Lambdin, Peru, Kansas. In a circular distributed by the manufacturer, it is stated that "I. G. O. is a saturated solution of Iodine Gas in petrolatum at 130 degrees with oil of eucalyptus. The heat of the body liberates the iodine and it is absorbed as free iodine."

A sample of I. G. O., received from a physician, was examined. It was found to be a black ointment, green in thin layers, with a slight odor like crude petroleum. By the methods used for the examination of Iodex, I. G. O. was found to contain 0.59 per cent. of free iodin.

INDEX TO VOLUME 12

The names of authors appear in capitals, under which will be found the titles of their signed articles. Under the names of the proprietors appear the respective products to which reference is made. The names of the products also occur in alphabetical sequence.

PAGE

Abbott Laboratories
    Barbital 10
    Barbital-Sodium 70
    Cinchophen 15
    Procain 17, 18
Acetates, in Williams' Rheumatic Treatment.................... 40
Acetylsalicylic Acid, Melting point of.................... 62
Acid, Behenic 98
    Benzoic, in Dr. De Sanctis' Rheumatic and Gout Pills.................... 47
    Boric, in Micajah's Medicated Uterine Wafers.................... 56
    Erucic 98
Acidol, and Acidol-Pepsin.................... 91
Acidol-Pepsin 91
    Tablets, examination of.................... 92
Acriflavine 64
    solubilities of 66
    tentative standards for.................... 68
Adamson bill 8
Alcohol, in Dr. Miles' Heart Treatment.................... 52
    in Lane's Asthma Cure.................... 35
Alkaloids, absence of in Dr. Miles' Heart Treatment.................... 53
    absence of, in Micajah's Suppositories for Hemorrhoids.................... 57
    test for in Nature's Remedy Tablets.................... 29
Aloes, in Nature's Remedy Tablets....................27, 28, 29
Alum, in Micajah's Medicated Uterine Wafer.................... 56
American Made Synthetic Drugs.................... 7
Ammonium Ichthyosulphonate, claimed ingredient in Micajah's Suppositories for Hemorrhoids.................... 56
Anglo-French Drug Co.
    Collosol cocain 33
    Collosols 42
    Cuprase 32
Apothesine 88
    examination of 88
    tentative standards for.................... 91
Arsenic, test for, in barium sulphate.................... 83
Atophan (see Cinchophen)
Balsam of Peru, claimed ingredient in Micajah's Suppositories for Hemorrhoids 56
Barbital, determination of in barbital-sodium.................... 74
    determination of uncombined in barbital-sodium.................... 77
    examination of 7

PAGE

Barbital-Sodium 11, 70
  Abbott, analysis of 73
Barbitone 70
Barium Compounds, soluble, in Barium Sulphate 81
  Sulphate 81
  Sulphate, analysis of 82
  Sulphid, in Depilagiene 31
Bayer & Co.
  Veronal 9
Belladonna, extract, a claimed ingredient in Micajah's Suppositories for Hemorrhoids 56
  root, in Nature's Remedy Tablets....................27, 29
Behenic Acid 98
Benzocain 88
Benzoic Acid in Dr. De Sanctis' Rheumatic and Gout Pills 47
Benzyl Benzoate 84
  analysis of 86
  tentative standards for 86
Betain hydrochlorid 91
Borax, in Micajah's Medicated Uterine Wafers 56
British Medical Research Committee Study of Acriflavine 64
Burdock, in Nature's Remedy Tablets 27
Cactus, supposed presence of, in Dr. Miles' Heart Treatment 51
Calcium in Lane's Asthma Cure 35
  determination of in Lane's Asthma Cure 36
  determination of in Sajodin 101
Calco Chemical Co.
  Cinchophen 15
  Procain 18
Cancer Cure, Gueth's 103
Caramel, detection of in Dr. Miles' Heart Treatment 52
Cascara, in Nature's Remedy Tablets....................27, 29
Cerelene 30
Chlorax 57
Chlorid, determination of in Lavoris 54
Chlorin compounds, in benzyl benzoate 85
  in Chloron, Chlorax and Number "3" 57
Chlorine Products Co., Inc.
  Chlorax 57
  Chloran 57
  Number "3" 57
Chloron, chlorax and Number "3" 57
Chinosol, Potassium sulphate in 88
  the examination of American Made 87
Cinchophen 7
  solubility of 16
Citronella, oil in Depilagiene 31
Chiris Antoine
  Barbital 10

PAGE
Clark, A. H.
    American Made Synthetic Drugs—II 7
    Barium Sulphate for Roentgen-Ray Work 81
    Iodin in liquid petrolatum 21
    Nature's Remedy Tablets 25
Cleaver, Edward
    Dr. De Sanctis' Rheumatic and Gout Pills 46
Cocain, in Collosol Cocain 34
Colchicum, in Dr. De Sanctis' Rheumatic and Gout Pills 46
Collosols 42
    argentum 43
    arsenicum 43
    Cocain 33, 44
    Cuprum 43
    Ferrum 43
    Hydrargyrum 43
    Iodin 44
    Manganese 43
    Quinin 44
    Sulphur 44
Copper in Cuprase 32
Cuprase 32
Curtis, Hal A.
    Sacred Bark, Root and Herb Compound 102
    Curtis' Sacred Bark, Root and Herb Compound 102
Dandelion, in Nature's Remedy Tablets 27
Depilagiene 31
Digitalis, supposed presence of, in Dr. Miles' Heart Treatment 51
Dr. De Sanctis' Rheumatic and Gout Pills 46
Dr. Miles' Heart Treatment 49
Drugs, American Made Synthetic 7
Ducatte Laboratories, F 32
Erucic Acid 98
Farbenfabriken vorm. Friedr. Bayer & Co.
    Sajodin 97
Farbwerke Hoechst Co.
    Holocain 12
Farbwerke, vorm. Meister Lucius & Bruening
    Sajodin 97
Federal Trade Commission
    Barbital 70
Federal Trade Commission, Drugs licensed by 7
Formaldehyd, detection of in Lavoris 55
Fougera, E. and Co.
    Dr. De Sanctis' Rheumatic and Gout Pills 46
Franco-American Co.
    Depilagiene 31
Franco-American Hygienic Depilagiene 31

PAGE

Gathercoal, E. N.
    Report on the microscopic examination of Nature's Remedy Tablets 26
Gout Pills, Dr. De Sanctis' Rheumatic.... 46
Gueth's Cancer Cure.... 103
Halter, V.
    Barbital 10
Heart Treatment, Dr. Miles'.... 49
Holliday Laboratories
    Cerelene 30
Holocain 7
Hynson, Westcott & Dunning
    Benzyl benzoate 84
Hypochlorite in Chloran, Chlorax and Number "3".... 57
I. G. O.... 106
Institute for Drug Research.... 20
Iodex and Liquid Iodex.... 104
Iodid, detemination of, in Lane's Asthma Treatment.... 37
    in Iodex 105
    in Sajodin 100
    in Liquid Iodex 106
    in liquid petrolatum.... 21
Iron, detection of, in Dr. Miles' Heart Treatment.... 52
    glycerophosphate, in Dr. Miles' Heart Treatment.... 52
Juniper berries, in Nature's Remedy Tablets.... 27
Lane, D. J.
    Lane's Asthma Cure.... 35
    Lane's Treatment 35
Lavoris Chemical Co.
    Lavoris 53
    Lavoris, former claims of composition.... 54
    Lavoris, modern claims of composition.... 54
Lead, determination of in Medinal.... 75
    determination of in Veronal-Sodium.... 75
Leech, Paul Nicholas
    American Made Synthetic Drugs, II.... 7
    Melting point of Acetylsalicylic Acid.... 62
Lewis Medicine Co.
    Nature's Remedy Tablets.... 25
Liquid Iodex 104
Liquid petrolatum, Parke, Davis & Co.... 23
Liquid petrolatum, Squibb.... 23
Loco weed disease.... 81
Luminal 77
    tentative standards for 78
Luminal-sodium 77
Luminal-sodium, tentative standards for.... 80
Mandrake, in Nature's Remedy Tablets.... 27
Medinal (see also Barbital-sodium)
Medinal 70

PAGE

Melting Point of Acetylsalicylic Acid.......................... 62
Menley and James
    Iodex and Liquid Iodex.......................... 104
Merck and Co.
    Veronal 9
Metz, H. A.
    Holocain 14
Micajah's Medicated Wafers.......................... 55
    Medicated Uterine Wafers.......................... 55
    Suppositories for Hemorrhoids.......................... 56
Miles' Heart Treatment, The Dr., garbled quotations from medical authorties 50
Miles Medicine Co.
    The Dr. Miles' Heart Treatment.......................... 49
Milliken & Co., J. T.
    Phenetidyl-acetphenetidin hydrochlorid 13
Milk sugar, in Dr. De Sanctis' Rheumatic and Gout Pills.......... 48
Morgenstern & Co.
    Cinchophen 15
Myricyl Palmitate, in Cerelene.......................... 30
Naming of Licensed Drugs.......................... 8
Note on a very old specimen of pepsin.......................... 23
Novocain (see Procain)
Number "3" 57
Orthoform, new 88
Parke, Davis & Co.
    Apothesine 89
Pepsin, a note on a very old specimen of.......................... 23
Phenetidylacetphenetidin hydrochlorid 7
Phenobarbital 77
Phenylcinchoninic Acid (see Cinchophen)
Phosphate, detection of in Dr. Miles' Heart Treatment............ 53
    test for, in barium sulphate.......................... 83
Pilocarpin hydrochlorid, relative permanency of in moist air as compared with pilocarpin nitrate.......................... 96
Podophyllum, resin of, in Nature's Remedy Tablets.............. 27
Potassium, in the Williams' Treatment.......................... 40
    bicarbonate, in the Williams' Rheumatic Treatment.......... 41
Prickly ash, in Nature's Remedy Tablets.......................... 27
Procain 89
    examination of 7
Proflavine 64
    solubilities of 66
    tentative standards for.......................... 69
Rabak, William
    American-Made Synthetic Drugs, II.......................... 7
Rector Chemical Co.
    Barbital 10
    Procain 18
Resorcin, absence of, in Lavoris.......................... 54

PAGE

Rhubarb, in Nature's Remedy Tablets ... 27
Rheumatic and Gout Pills, Dr. De Sanctis' ... 46
  Treatment, the Dr. D. A. Williams' ... 37
Saccharin, detection of in Lavoris ... 55
Sacred Bark, Root and Herb Compound, Curtis' ... 102
Sajodin ... 97
    analysis of ... 99
    tablets of ... 101
    tablets, tentative standards for ... 102
    tentative standards for ... 99
Sanguinaria, in Gueth's Cancer Cure ... 103
Sarsaparilla, alleged ingredient, in Nature's Remedy Tablets ... 27
Schering & Glatz
    Atophan ... 13
    Medinal ... 70
Sodium, determination of in barbital-sodium ... 73
    Dioxide, Dental ... 93
    hydroxid, estimation of in Sodium Dioxide Dental ... 94
    peroxid, determination of in Sodium Dioxide Dental ... 94
Solubility of Cinchophen ... 16
Stanolind ... 23
Sugar in Lane's Asthma Cure ... 35
Sulphate, in proflavine ... 67
Sulphur in Depilagiene ... 31
Suppositories, Micajah's ... 55
Sweet & Co., W. H.
    Cinchophen ... 15
Synthetic Drugs, American-Made ... 7
Synthetic Products Co.
    Holocain ... 14
Trypaflavine ... 64
Veronal (see Barbital)
Veronal-sodium ... 70
Wafers, Micajah's ... 55
Warren, L. E.
    A Note on a Very Old Specimen of Pepsin ... 23
    Examination of Acriflavine and Proflavine ... 64
    Examination of Commecial Barbital-Sodium ... 70
    Examination of Luminal and Luminal-Sodium ... 77
Williams, The D. A. Co.
    The Williams' Treatment ... 37
Winthrop Chemical Co.
    Sajodin ... 98
    Veronal-Sodium ... 70
Zinc, determination of, in Lavoris ... 54

Department
of
Pharmacology
University
of
Toronto

Department
of
Pharmacology
University
of
Toronto